MINISTRY OF HEALTH OF UKRAINE
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY

METHODICAL RECOMMENDATIONS

FOR PREPARING TO PRACTICAL CLASSES FROM DISCIPLINE "ONCOLOGY"

PART I

FOR THE FOREIGN STUDENTS OF HIGHER MEDICAL INSTITUTIONS OF UKRAINE OF THE III–IV ACCREDITATION LEVELS

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CONTENT

ПЕРЕДМОВА

Вашій увазі пропонується пакет методичних розробок практичних занять з онкології розроблений у відповідності до навчальних планів та програм навчальної дисципліни «Онкологія» для студентів медичних навчальних закладів III-IV рівнів акредитації за спеціальністю 7.110101 «Лікувальна справа», за якими чужоземні, в т.ч. англомовні, студенти проходять курс «Онкологія».

Навчальна програма передбачає 90 годин занять: 10 – лекційних, 40 – практичних занять та 40 годин самостійної роботи. За час навчання студентам для вивчення тематики виділено 8 практичних занять по 5 годин.

Розроблений кафедрою онкології та радіології пакет методичних розробок для практичних занять з онкології, що стосується практично усіх важливих питань сучасної клінічної онкології націлює студентів на розвиток клінічного мислення і отримання високих професійних знань, що сприятиме у подальшому формуванню професійних вмінь і навичок.

При створенні посібника використано матеріали як вітчизняних авторів, призначені для користувякання англомовними студентами, так і зарубіжних (зокрема DeVita V.T., Lawrence T.S., Rosenberg S.A. Cancer Principles & Practice of Oncology, 10th ed., 2015), останню (7-му) класисифікацію TNM (Sobin L.H., Gospodarowicz M.K., Wittekind C. TNM Classification of Malignant Tumors, 7th ed., 2010) та матеріали «Вікіпедія».

Посібник призначений для внутрішнього користування.

PREFACE

We offer a package of teaching materials for practical classes from discipline “Oncology” designed in accordance with the curriculum and discipline program "Oncology" for students of medical educational institutions of III-IV accreditation levels in specialty 7.110101 "General medicine", according which foreign, including English-speaking, students take the course "Oncology".

The training program provides 90 hours of classes: 10 – lecture, 40 – plactical classes and 40 hours of self-work. During trainings to explore topics students had 8 practical classes for 5 hours each.

Developed by the Department of Oncology and Radiology package of teaching materials for practical classes in oncology concerning almost all important issues of modern clinical oncology and directs students in the development of clinical thinking and obtaining high professional knowledge that will contribute to further formation of professional skills.

During creation the manual there were used materials of Ukrainian authors designed for English-speaking students and foreign authors (including DeVita V.T., Lawrence T.S., Rosenberg S.A. Cancer Principles & Practice of Oncology, 10th ed., 2015), the last TNM classification of tumors (Sobin L.H., Gospodarowicz M.K., Wittekind C. TNM Classification of Malignant Tumors, 7th ed., 2010) and materials of "Wikipedia".

The manual is intended for internal use.

THEME 1

SKIN CANCER. MELANOMA

MELANOMA

1.1. EPIDEMIOLOGY

Malignant melanoma is the sixth most common U.S. cancer diagnosis. The actual incidence of melanoma is increasing more rapidly than that of any other malignancy, with 68,130 cases of invasive melanoma and 8,700 melanoma deaths in the United States in 2009, and with 16,900 cases of invasive melanoma annually in developed countries globally. This amounts to 4% of new cancer diagnoses and 1.5 % of cancer deaths. In the early part of the twentieth century, the lifetime risk of a white person developing melanoma was approximately 1 in 1,500. Currently this risk is approximately 1 in 56 for women and 1 in 37 for men. Its incidence is second only to breast cancer for women from birth to age 39 years; similarly, it is the second most common cancer diagnosis for men through age 39 years, slightly less common than leukemia. Despite general physician awareness and excellent public education, this malignancy still has an approximate 14% mortality in the United States, and for patients who present with regional and distant metastases, the 5-year mortality rates are approximately 38% and 85%, respectively. Overall 5-year survival rates for melanoma have increased from 82% in the late 1970s (1975 to 1977) to 91% in the more recent era (2002 to 2006).

This is a disease that disproportionately affects whites over African American, Asian, or other dark-skinned individuals. In the United States, whites account for 98.2% of cutaneous melanomas reported in the National Cancer Database, with African Americans accounting for 0.7% and Hispanics accounting for 1.1 %. This is best explained by a combined effect of ultraviolet (UV) sunlight exposure and fair skin. It is most striking that the highest per-capita incidence of melanoma worldwide is in Australia, and that this high incidence afflicts primarily the Australians of Western European descent who have fair skin, and not the darker-skinned aboriginal population. It is also notable that these fair-skinned European descendants who moved to Australia have much higher incidences of melanoma than the Western European populations that remain in the higher latitudes of Europe. In migrant populations, individuals who move during childhood to areas with greater sun exposure develop melanoma at rates higher than those of their country of origin and similar to those of their adopted country.

In nonwhite populations, there is a much higher proportion of melanomas in acral (subungual, palmar, plantar) and mucosal locations. However, the incidences of those types of melanoma are similar across races. Their higher relative proportion in Asians and African Americans can be best explained by the disproportionate increase in nonacral cutaneous melanomas in fair-skinned whites rather than by an absolute increase in risk of acral and mucosa! melanomas in nonwhite populations.

Ocular and nonacral cutaneous melanomas are 50- to 200-fold more likely in white populations than in nonwhite populations, but melanomas in acral and mucosal sites are within twofold of each other across racial groups . Similarly, the increased incidence of melanoma over the last few decades can be explained primarily by increased incidence in white populations, not in nonwhite populations. These observations support the hypothesis that most cutaneous melanomas in white populations are etiologically related to sun exposure but that there may be a baseline risk of melanoma in other locations that is unrelated to sun damage. Recent data suggest significant molecular differences between acral melanomas and melanomas arising on the skin associated with chronic sun damage, with B-RAF and N-RAS mutations in 81 % of melanomas on chronically sun-damaged skin, whereas those mutations were uncommon in melanomas from acral or mucosal sites or from skin without chronic sun damage.

1.2. ETIOLOGY, RISK FACTORS

The demographic features of melanoma have implicated UV light exposure as a major etiologic factor in the development of melanoma. Multiple studies continue to support an etiologic association between UV irradiation and melanoma. Ultraviolet C radiation is generally absorbed by the ozone layer. Ultraviolet-B (UVB) radiation (290 to 320 nm) is associated with sunburn and induction of tanning by melanin pigment production. There are substantial data to support its etiologic role in melanoma. There is also some evidence implicating UVA radiation (320 to 400 nm), although UVA is more associated with chronic sun damage changes. However, the relative role of each type of UV irradiation in melanoma etiology is debated. Some animal data suggest that sun exposure early in life increases the risk o f melanoma. Human skin grafted on mice will develop nevi and melanomas in the presence of UVB irradiation, further supporting the role of UVB irradiation and melanoma. Burns early in life have been implicated in melanoma incidence. However, chronic sun exposure in individuals who tan may even protect against melanoma. Considering these o b servations, plus the epidemiology described earlier, suggests that the etiology of many, if not most, cutaneous melanomas appears to be associated with a combination of fair skin that burns easily and high UV/sun exposure. The role of sunlight intensity and frequency is debated, but both chronic and intermittent exposure may be relevant. Current data suggest that UV radiation causes melanoma by a combination of DNA damage, inflammation, and immune suppression.

Tanning bed use has been implicated in the etiology of melanoma, with a recent report that any tanning bed use in adolescence or early adulthood is associated with a 1.4-fold increase in melanoma incidence, and that this relative risk increases to 2.0 for individuals with at least ten tanning bed sessions. The association was most significant for the risk of melanoma diagnosed at ages 30 to 39.

Tanning bed use has been formally classified as a carcinogen, and increased awareness of the harmful effects of UV exposure promise to control the increase in melanoma incidence. However, this has highlighted another growing health concern, that without sun exposure, there is an increasing rate of vitamin D deficiency. It has been estimated that increasing UVB exposure to allow mean serum hydroxyvitamin D levels to 45 ng/mL would lead to preventing almost 400,000 deaths per year from cardiovascular diseases and cancer, although at the price of increasing melanoma mortality by several thousand deaths per year. Thus, questions remain about the optimal UV exposure and how to optimize vitamin D levels.

Another factor that may increase the risk of melanoma is a heritable predisposition. This may explain a minority of melanomas (e.g., 5% to 10%). Mutations associated with melanoma risk include inactivation of two critical tumor suppression pathways-that mediated through p16/CDK4 and CDK6/retinoblastoma gene, and that mediated through p14 and p53. Mutations of CDKN2a have also been identified in 25% to 50% of melanoma kindreds studied.

Other common risk factors include dysplastic nevus syndrome, a history of other skin cancers associated with sun exposure, and a family history of melanoma. Xeroderma pigmentosum also is associated with increased melanoma risk, but it is uncommon. Higher socioeconomic status is also associated with higher risk.

Radiation doses greater than 15 Gy delivered to pediatric oncology patients has been shown to increase the risk of developing malignant melanoma by an odds ratio of 13.

1.3. BIOLOGY

Atypical melanocytes arising in a pre-existing nevus or de nova are very common but rarely progress to melanoma. However, some patients develop confluent atypical melanocytic hyperplasia at the dermal/epidermal j unction or nests of atypical melanocytes in the epidermis or at the dermal/epidermal junction. As this process progresses, it reaches a point at which it warrants a diagnosis of melanoma. However, early melanomas usually proceed to grow radially, and this is called the radial growth phase (RGP) of melanoma, which may continue for years before progressing to the vertical growth phase (VGP).

The RGP of a cutaneous melanoma may include either melanoma in situ or superficial invasion into the papillary dermis, or both. Melanomas in RGP present clinically as enlarging macules or very minimally raised papular lesions, which are typically (but not always) pigmented. These lesions are rarely symptomatic. This is the ideal time to diagnose melanoma, and the changing nature of these RGP lesions often is adequate for recognition by the patient and by the clinician. However, if not recognized, these lesions typically progress to the VGP, manifest clinically by a nodular growth of the lesion, often described by the patient as a lesion that began to "raise up".

RGP melanomas have very low metastatic capacity. It has been reported that the risk of subsequent metastasis from RGP lesions is zero, but several case reports illustrate exceptions to that observation. Nonetheless, RGP melanomas are associated with an excellent prognosis and mortality risk at the low end of the 0% to 5% range. There is often a substantial window of time between the appearance of clinically detectable RGP and development of VGP-on the order of months to years-during which there is opportunity for curative discovery and excision of early melanoma.

However, a s melanomas develop VGP, they acquire increased metastatic risk. Thus, risk of melanoma progression is most associated with the presence of VGP, the depth of invasion, and other markers of the malignant phenotype in the VGP component of a melanoma. On the other hand, the extent of RGP (e.g., clinically, the diameter of the skin lesion) and multiplicity of RGP lesions are not associated with significant risk of metastasis or melanoma-associated mortality.

Unfortunately, some melanomas are nonpigmented and escape early diagnosis for that reason. Others develop a VGP in the absence of a RGP (nodular melanoma histology), and the time course of progression in these lesions does not afford the same interval for early diagnosis that is observed in melanomas with a preceding RGP component (superficial spreading melanoma, lentigo maligna melanoma, lentiginous melanoma, acral lentiginous melanoma). Finally, some melanomas present as metastatic melanoma in lymph nodes, skin, subcutaneous tissue, or visceral sites without an apparent primary cutaneous site. In some cases, these have been associated with a history of a regressed primary melanocytic lesion. In other cases, such an explanation is less clear. In all of these cases, the prospect of early diagnosis of melanoma is compromised, and the risk of melanoma-associated mortality is increased. Thus, there is still substantial need for more accurate diagnostic methods and more effective screening practices for this difficult disease.

1.4. PREVENTION AND SCREENING

Advanced melanoma has a very poor prognosis. However, melanomas diagnosed and treated during the RGP have an excellent prognosis. Thus, prevention and early diagnosis can have a great impact on decreasing melanoma morbidity and mortality. The apparent leveling off of melanoma-related mortality rates in Australia and the United States likely is the result of better screening and prevention.

Sun exposure

Ultraviolet exposure and sunburns, in particular, appear to be etiologic in most melanomas. Thus, protection from UV light, especially in fair-skinned individuals, is believed to have substantial benefit in preventing melanoma. Although many people tend to think of sunscreens when they think of sun protection, there is no formal proof that sunscreens prevent melanoma. There also are some limitations inherent in sunscreen use.

One is that certain body sites are not easily covered with sunscreen, such as the scalp. More important, even " waterproof" sunscreens wash off or become less effective with time. Most people also forget to reapply sunscreens frequently enough and may still get burns. There are also sociological issues, which may differ for different populations and are arguable. However, it is worth considering the provocative findings of a study performed on young adults from Western Europe, who were randomized to receive either sun protection factor (SPF) 10 or SPF 30 sunscreen. In a blinded fashion, they were asked to report sun exposure times and sunburns. The number of sunburns was the same in both groups, and sun exposure was greater in the SPF 30 group, suggesting that some populations may stay in the sun until they get a burn, and that sunscreen simply helps them
to stay in the sun longer.

It is safe to say that the best protection from the sun is a building, the next best is protective clothing, and the third best is sunscreen. Patients should be advised to use all three. Avoiding midday sun from about 11 AM to 3 PM by staying indoors is advised, as well as wearing clothing with a thick enough weave that it blocks sunlight, or a formal SPF rating, when possible. Hats are particularly helpful for the face and scalp, which often are highly exposed to sunlight and not so readily covered fully with sunscreen. Otherwise, sunscreen can provide protection to sun-exposed areas when outside

Self-Examination

For many patients, they, their spouses, or other family members may be able to screen effectively for new suspicious skin lesions, and this should be encouraged. It is more common for women to detect melanomas than for men to do so, either for themselves or for their partners. In any case, there is value in educating patients about how to detect melanomas if they are at high risk. As many as half of melanomas are identified by the patient or family, and patient self-examination has been associated with diagnosis of thinner melanomas. In a study by Berwick et al., patients performing self-examination appeared to have melanomas that were detected in an earlier microstage. Teaching aids for patients on how to perform skin self-examination are available from the American Cancer Society and the American Academy of Dermatology. Patients with melanoma or at high risk should be seen regularly by a dermatologist. It is reasonable to suggest that patients perform skin self-examinations more often than their dermatology visits, although there are no proven guidelines. Doing a self-examination once a month may be the easiest for the patient to remember.

1.5. DIAGNOSIS OF PRIMARY MELANOMA

Visual diagnosis of melanomas is still the most common method employed by health professionals. Moles that are irregular in color or shape are often treated as candidates of melanoma. The diagnosis of melanoma requires experience, as early stages may look identical to harmless moles or not have any color at all. People with a personal or family history of skin cancer or of dysplastic nevus syndrome (multiple atypical moles) should see a dermatologist at least once a year to be sure they are not developing melanoma. There is no blood test for detecting melanomas.

To detect melanomas (and increase survival rates), it is recommended to learn what they look like, to be aware of moles and check for changes (shape, size, color, itching or bleeding) and to show any suspicious moles to a doctor with an interest and skills in skin malignancy.

A popular method for remembering the signs and symptoms of melanoma is the mnemonic "ABCDE":

- **A**symmetrical skin lesion.
- **B**order of the lesion is irregular.
- **C**olor: melanomas usually have multiple colors.
- **D**iameter: moles greater than 6 mm are more likely to be melanomas than smaller moles.
- **E**nlarging: Enlarging or evolving

A weakness in this system is the diameter. Many melanomas present themselves as lesions smaller than 6 mm in diameter; and all melanomas were malignant on day 1 of growth, which is merely a dot. An astute physician will examine all abnormal moles, including ones less than 6 mm in diameter. Seborrheic keratosis may meet some or all of the ABCD criteria, and can lead to false alarms among laypeople and sometimes even physicians. An experienced doctor can generally distinguish seborrheic keratosis from melanoma upon examination, or with dermatoscopy.

Some advocate the system "ABCDE", with E for evolution. Certainly moles that change and evolve will be a concern. Alternatively, some refer to E as elevation. Elevation can help identify a melanoma, but lack of elevation does not mean that the lesion is not a melanoma. Most melanomas are detected in the very early stage, or in-situ stage, before they become elevated. By the time elevation is visible, they may have progressed to the more dangerous invasive stage.

Nodular melanomas do not fulfill these criteria, having their own mnemonic, "EFG":

- **E**levated: the lesion is raised above the surrounding skin.
- **F**irm: the nodule is solid to the touch.
- **G**rowing: the nodule is increasing in size.

Following a visual examination and a dermatoscopic exam, or in vivo diagnostic tools such as a confocal microscope, the doctor may biopsy the suspicious mole. A skin biopsy performed under local anesthesia is often required to assist in making or confirming the diagnosis and in defining the severity of the melanoma. If the mole is malignant, the mole and an area around it need excision. Elliptical excisional biopsies may remove the tumor, followed by histological analysis and Breslow scoring. Punch biopsies are contraindicated in suspected melanomas, for fear of seeding tumour cells and hastening the spread of the malignant cells.

Total body photography, which involves photographic documentation of as much body surface as possible, is often used during follow-up of high-risk patients. The technique has been reported to enable early detection and provides a cost-effective approach (being possible with the use of any digital camera), but its efficacy has been questioned due to its inability to detect macroscopic changes.

1.6. TNM-CLASSIFICATION

Nowadays are used 7th edition of TNM-classification (UICC + AJCC)

T – Primary Tumour

The extent of the tumour is classified after excision

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in one regional lymph node
N1a Only microscopic metastasis (clinically occult)
N1b Macroscopic metastasis (clinically apparent)
N2 Metastasis in two or three regional lymph nodes or satellite(s) or in-transit metastasis
N2a Only microscopic nodal metastasis
N2b Macroscopic nodal metastasis
N2c Satellite(s) or in-transit metastasis without regional nodal metastasis
N3 Metastasis in four or more regional lymph nodes, or matted metastatic regional lymph nodes, or satellite or in-transit metastasis with metastasis in regional lymph node(s)

Note: *Satellites are tumour nests or nodules (macro- or microscopic) within 2 cm of the primary tumour. In-transit metastasis involves skin or subcutaneous tissue more than 2 cm from the primary tumour but not beyond the regional lymph nodes.*

M – Distant Metastasis

M0 No distant metastasis
M1 Distant metastasis
M1a Skin, subcutaneous tissue or lymph node(s) beyond the regional lymph nodes
M1b Lung
M1c Other sites, or any site with elevated serum lactic dehydrogenase (LDH)

pT – Primary Tumour

pTX Primary tumour cannot be assessed*
pT0 No evidence of primary tumour
pTis Melanoma in situ (Clark Level I) (atypical melanocytic hyperplasia, severe melanocytic dysplasia, not an invasive malignant lesion)

Note: **pTX includes shave biopsies and regressed melanomas.*

pT1 Tumour 1 mm or less in thickness
pT1a Clark level II or III, without ulceration
pT1b Clark Level IV or V, or with ulceration
pT2 Tumour more than 1 mm but not more than 2 mm in thickness
pT2a without ulceration
pT2b with ulceration
pT3 Tumour more than 2 mm but not more than 4 mm in thickness
pT3a without ulceration
pT3b with ulceration
pT4 Tumour more than 4 mm in thickness
pT4a without ulceration
pT4b with ulceration

Grouping for stages			
Stage	**pT**	**N**	**M**
0	pTis	N0	M0
IA	pT1a	N0	M0
IB	pT1b	N0	M0
	pT2a	N0	M0
IIA	pT2b	N0	M0
	pT3a	N0	M0
IIB	pT3b	N0	M0
	pT4a	N0	M0
IIC	pT4b	N0	M0
IIIA	pT1-4a	N1a	M0
	pT1-4a	N2a	M0
IIIB	pT1-4a	N1b	M0
	pT1-4a	N2b	M0
	pT1-4a	N2c	M0
	pT1-4b	N1a	M0
	pT1-4b	N2a	M0
	pT1-4b	N2c	M0
IIIC	pT1-4b	N1b	M0
	pT1-4b	N2b	M0
	Any pT	N3	M0
IV	Any pT	Any N	M1

In clinics melanoma sometimes is divided into the following clinical types:

- Lentigomaligna
- Lentigomaligna melanoma
- Superficial spreading melanoma
- Acrallentiginous melanoma
- Mucosal melanoma
- Nodular melanoma
- Polypoid melanoma
- Desmoplastic melanoma
- Amelanotic melanoma
- Soft-tissue melanoma

1.7. LABORATORY TESTS

Lactate dehydrogenase (LDH) tests are often used to screen for metastases, although many patients with metastases (even end-stage) have a normal LDH; extraordinarily high LDH often indicates metastatic spread of the disease to the liver. It is common for patients diagnosed with melanoma to have chest X-rays and an LDH test, and in some cases CT, MRI, PET and/or PET/CT scans. Although controversial, sentinel lymph node biopsies and examination of the lymph nodes are also performed in patients to assess spread to the lymph nodes. A diagnosis of melanoma is supported by the presence of the S-100 protein marker.

1.8. TREATMENT

Confirmation of the clinical diagnosis is done with a skin biopsy. This is usually followed up with a wider excision of the scar or tumor. Depending on the stage, a sentinel lymph node biopsy is done, as well, although controversy exists around trial evidence for this procedure. Treatment of advanced malignant melanoma is performed from a multidisciplinary approach.

Surgery

Excisional biopsies may remove the tumor, but further surgery is often necessary to reduce the risk of recurrence. Complete surgical excision with adequate surgical margins and assessment for the presence of detectable metastatic disease along with short- and long-term followup is standard. Often this is done by a wide local excision (WLE) with 1 to 2 cm margins. Melanoma-in-situ and lentigomalignas are treated with narrower surgical margins, usually 0.2 to 0.5 cm. Many surgeons consider 0.5 cm the standard of care for standard excision of melanoma-in-situ, but 0.2 cm margin might be acceptable for margin controlled surgery (Mohs surgery, or the double-bladed technique with margin control).

The wide excision aims to reduce the rate of tumour recurrence at the site of the original lesion. This is a common pattern of treatment failure in melanoma. Considerable research has aimed to elucidate appropriate margins for excision with a general trend toward less aggressive treatment during the last decades.

Mohs surgery has been reported with cure rate as low as 77% and as high as 98% for melanoma-in-situ. CCPDMA and the "double scalpel" peripheral margin controlled surgery is equivalent to Mohs surgery in effectiveness on this "intra-epithelial" type of melanoma.

Melanomas that spread usually do so to the lymph nodes in the area of the tumor before spreading elsewhere. Attempts to improve survival by removing lymph nodes surgically (lymphadenectomy) were associated with many complications, but no overall survival benefit. Recently, the technique of sentinel lymph node biopsy has been developed to reduce the complications of lymph node surgery while allowing assessment of the involvement of nodes with tumor.

Although controversial and without prolonging survival, sentinel lymph node biopsy is often performed, especially for T1b/T2+ tumors, mucosal tumors, ocular melanoma and tumors of the limbs. A process called lymphoscintigraphy is performed in which a radioactive tracer is injected at the tumor site to localize the sentinel node(s). Further precision is provided using a blue tracer dye, and surgery is performed to biopsy the node(s). Routine hematoxylin and eosin (H&E) and immunoperoxidase staining will be adequate to rule out node involvement. Polymerase chain reaction (PCR) tests on nodes, usually performed to test for entry into clinical trials, now demonstrate that many patients with a negative sentinel lymph node actually had a small number of positive cells in their nodes. Alternatively, a fine-needle aspiration biopsy may be performed and is often used to test masses.

If a lymph node is positive, depending on the extent of lymph node spread, a radical lymph node dissection will often be performed. If the disease is completely resected, the patient will be considered for adjuvant therapy. Excisional skin biopsy is the management of choice. Here, the suspect lesion is totally removed with an adequate (but minimal, usually 1 or 2 mm) ellipse of surrounding skin and tissue. To avoid disruption of the local lymphatic drainage, the preferred surgical margin for the initial biopsy should be narrow (1 mm). The biopsy should include the epidermal, dermal, and subcutaneous layers of the skin. This enables the histopathologist to determine the thickness of the melanoma by microscopic examination. This is described by Breslow's thickness (measured in millimeters). However, for large lesions, such as suspected lentigomaligna, or for lesions in surgically difficult areas (face, toes, fingers, eyelids), a small punch biopsy in representative areas will give adequate information and will not disrupt the final staging or depth determination. In no circumstances should the initial biopsy include the final surgical margin (0.5 cm, 1.0 cm, or 2 cm), as a misdiagnosis can result in excessive scarring and morbidity from the procedure. A large initial excision will disrupt the local lymphatic drainage

and can affect further lymphangiogram-directed lymphnode dissection. A small punch biopsy can be used at any time where for logistical and personal reasons a patient refuses more invasive excisional biopsy. Small punch biopsies are minimally invasive and heal quickly, usually without noticeable scarring.

Adjuvant treatment

High-risk melanomas may require adjuvant treatment, although attitudes to this vary in different countries. In the United States, most patients in otherwise good health will begin up to a year of high-dose interferon treatment, which has severe side effects, but may improve the patient's prognosis slightly. However British Association of Dermatologist guidelines on melanoma state that interferon is not recommended as a standard adjuvant treatment for melanoma. A 2011 meta-analysis showed that interferon could lengthen the time before a melanoma comes back but increased survival by only 3% at 5 years. The unpleasant side effects also greatly decrease quality of life.

In Europe, interferon is usually not used outside the scope of clinical trials.

Metastatic melanomas can be detected by X-rays, CT scans, MRIs, PET and PET/CTs, ultrasound, LDH testing and photoacoustic detection.

Chemotherapy and immunotherapy

Various chemotherapy agents are used, including dacarbazine (also termed DTIC), immunotherapy (with interleukin-2 (IL-2) or interferon (IFN)), as well as local perfusion, are used by different centers. The overall success in metastatic melanoma is quite limited. IL-2 (Proleukin) is the first new therapy approved for the treatment of metastatic melanoma in 20 years. Studies have demonstrated that IL-2 offers the possibility of a complete and long-lasting remission in this disease, although only in a small percentage of patients. A number of new agents and novel approaches are under evaluation and show promise. Clinical trial participation should be considered the standard of care for metastatic melanoma.

Radiation therapy

Radiation therapy is often used after surgical resection for patients with locally or regionally advanced melanoma or for patients with unresectable distant metastases. It may reduce the rate of local recurrence but does not prolong survival.Radioimmunotherapy of metastatic melanoma is currently under investigation. Radiotherapy has a role in the palliation of metastatic melanoma.

1.9. PROGNOSIS

Features that affect prognosis are tumor thickness in millimeters (Breslow's depth), depth related to skin structures (Clark level), type of melanoma, presence of ulceration, presence of lymphatic/perineural invasion, presence of tumor-infiltrating lymphocytes (if present, prognosis is better), location of lesion, presence of satellite lesions, and presence of regional or distant metastasis. Certain types of melanoma have worse prognoses but this is explained by their thickness. Interestingly, less invasive melanomas even with lymph node metastases carry a better prognosis than deep melanomas without regional metastasis at time of staging. Local recurrences tend to behave similarly to a primary unless they are at the site of a wide local excision (as opposed to a staged excision or punch/shave excision) since these recurrences tend to indicate lymphatic invasion.

When melanomas have spread to the lymph nodes, one of the most important factors is the number of nodes with malignancy. Extent of malignancy within a node is also important; micrometastases in which malignancy is only microscopic have a more favorable prognosis than macrometastases. In some cases micrometastases may only be detected by special staining, and if malignancy is only detectable by a rarely employed test known as the polymerase chain reaction (PCR), the prognosis is better. Macrometastases in which malignancy is clinically apparent (in some cases cancer completely replaces a node) have a far worse prognosis, and if nodes are matted or if there is extracapsular extension, the prognosis is still worse.

When there is distant metastasis, the cancer is generally considered incurable. The five year survival rate is less than 10%. The median survival is 6 to 12 months. Treatment is palliative, focusing on life-extension and quality of life. In some cases, patients may live many months or even years with metastatic melanoma (depending on the aggressiveness of the treatment). Metastases to skin and lungs have a better prognosis. Metastases to brain, bone and liver are associated with a worse prognosis.

There is not enough definitive evidence to adequately stage, and thus give a prognosis for ocular melanoma and melanoma of soft parts, or mucosal melanoma (e.g. rectal melanoma), although these tend to metastasize more easily. Even though regression may increase survival, when a melanoma has regressed, it is impossible to know its original size and thus the original tumor is often worse than a pathology report might indicate.

1.10. FURTHER RESEARCH

Pharmacotherapy research for unresectable or metastatic malignant melanoma offers new treatment possibilities. In addition to the advances with recently approved agents, ongoing research into combination therapy, such as dabrafenib and trametinib, may reveal a more effective and better-tolerated option for patients with metastatic melanoma.

One important pathway in melanin synthesis involves the transcription factor MITF. The MITF gene is highly conserved and is found in people, mice, birds, and even fish. MITF production is regulated via a fairly straightforward pathway. UV radiation causes increased expression of transcription factor p53 in keratinocytes, and p53 causes these cells to produce melanocyte-stimulating hormone (MSH), which binds to melanocortin 1 receptors (MC1R) on melanocytes. Ligand-binding at MC1R receptors activates adenylatecyclases, which produce cAMP, which activates CREB, which promote MITF expression. The targets of MITF include p16 (a CDK inhibitor) and Bcl2, a gene essential to melanocyte survival. It is often difficult to design drugs that interfere with transcription factors, but perhaps new drugs will be discovered that can impede some reaction in the pathway upstream of MITF.

Studies of chromatin structure also promise to shed light on transcriptional regulation in melanoma cells. It has long been assumed that nucleosomes are positioned randomly on DNA, but murine studies of genes involved in melanin production now suggest that nucleosomes are stereotypically positioned on DNA. When a gene is undergoing transcription, its transcription start site is almost always nucleosome-free. When the gene is silent, however, nucleosomes often block the transcriptional start site, suggesting that nucleosome position may play a role in gene regulation.

Finally, given the fact that melanin helps protect skin cells from UV-induced damage, new melanoma prevention strategies could involve attempts to induce melanin synthesis in individuals who would otherwise get sunburns. Redheads, for example, do not tan because they have MC1R mutations. In mice, it has been shown that the melanin production pathway can be rescued downstream of MC1R.

A study published on January 27, 2011, by M. RazaZaidi et al. shows that interferon-γ links ultraviolet radiation to melanomagenesis in mice. Using a mouse model that allowed the visual tracking and purification of melanocytes using a green fluorescent dye, data showed that UVB-induced, macrophage-enhanced interferon-γ release results in melanoma growth, proliferation and immunoevasion. Based on these results, the interferon-γ pathway can potentially serve as part of new therapeutic measures to treat patients suffering from malignant melanoma, as well as a potential preventive strategy against UV-induced radiation.

BRAF

About 60% of melanomas contain a mutation in the B-Raf gene. Early clinical trials suggested that B-Raf inhibitors including Plexxicon'svemurafenib could lead to substantial tumor regression in a majority of patients if their tumor contain the B-Raf mutation. In June 2011, a large clinical trial confirmed the positive findings from those earlier trials.

In June 2012 a study reported that patients taking a different B-Raf inhibitor, Dabrafenib, did better than patients taking a chemotherapy agent.

Some researchers believe that combination therapies that simultaneously block multiple pathways may improve efficacy by making it more difficult for the tumor cells to mutate before being destroyed. In October 2012 a study reported that combining Dabrafenib with a MEK inhibitor led to even better outcomes. Compared to Dabrafenib alone, progression-free survival was increased to 41% from 9%, and the median progression-free survival increased to 9.4 months versus 5.8 months. Some side effects were, however, increased in the combined study.

Ipilimumab

At the American Society of Clinical Oncology Conference in June 2010, the Bristol-Myers Squibb pharmaceutical company reported the clinical findings of their drug ipilimumab. The study found an increase in median survival from 6.4 to 10 months in patients with advanced melanomas treated with the monoclonal ipilimumab, versus an experimental vaccine. It also found a one year survival rate of 25% in the control group using the vaccine, 44% in the vaccine and ipilimumab group, and 46% in the group treated with ipilimumab alone. However, some have raised concerns about this study for its use of the unconventional control arm, rather than comparing the drug against a placebo or standard treatment. The criticism was that although Ipilimumab performed better than the vaccine, the vaccine has not been tested before and may be causing toxicity, making the drug appear better by comparison.

In June 2011, a clinical trial of ipilimumab plus dacarbazine combined this immune system booster with the standard chemotherapy drug that targets cell division. It showed an increase in median survival for these late stage patients to 11 months instead of the 9 months normally seen.

Researchers were also hopeful that perhaps 10–20% of patients could live a long time. Some serious side-effects of revving up the immune system were seen in some patients. A course of treatment costs $120,000. The drug's brandname is Yervoy.

Targeted therapies

In clinical research setting other therapies, such as adoptive cell therapy or gene therapy, may be tested. Two kinds of experimental treatments developed at the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the US, have been used in advanced (metastatic) melanoma with high success rates in terms of melanoma treatments. The first treatment involves adoptive cell therapy (ACT) using TILs immune cells (tumor infiltrating lymphocytes) isolated from a patient's own melanoma tumor. These cells are grown in large numbers in a laboratory and returned to the patient after a treatment that temporarily reduces normal T cells in the patient's body. TIL therapy following lymphodepletion can result in durable complete response in a variety of setups.

Up to date, the only medical center outside the USA that has managed to successfully implement this technology is Sheba Medical Center through "Ella Institute of Melanoma", found in Israel (objective response rates of 50%). The second treatment, adoptive transfer of genetically altered autologous lymphocytes, depends on delivering genes that encode so called T cell receptors (TCRs), into patient's lymphocytes. After that manipulation lymphocytes recognize and bind to certain molecules found on the surface of melanoma cells and kill them.
A new treatment that trains the immune system to fight cancer has shown modest benefit in late-stage testing against melanoma. Sutent may be effective for patients with metastatic melanoma.

1.11. QUESTIONS FOR SELF-CONTROL

1. What is basal cell carcinoma (BCC), it`s causes, common sites and clinical signs?
2. What is squamous cell carcinoma (SCC), it`s causes, common sites and clinical signs?
3. Name three differences between BCC and SCC.
4. What does ABCDE stand for?
5. Name 2 types of melanoma staging methods (generally used).
6. Name the types of surgeries used in the treatment of skin malignant melanoma.

1.12. TESTS FOR SELF-CONTROL

Choose the one correct answer:

1. The most common cutaneous malignancy in humans is:
    a. Squamous cell carcinoma
    b. Mixed carcinoma
    c. Metatypic carcinoma
    d. Basal cell carcinoma
2. Factors that can cause skin cancer:
    a. Insolation
    b. Thermal burns
    c. Radioactive irradiation
    d. All above mentioned
3. Morphologic diagnoses of melanoma is:
    a. Aspiration biopsy
    b. Incisional biopsy
    c. Excisional biopsy
    d. Tumor prints

4. The greatest number of skin cancer-related deaths worldwide is associated with:
    a. Melanoma
    b. Basal cell carcinoma
    c. Squamous cell carcinoma
    d. Kaposi`s sarcoma
5. A shave biopsyin melanomas is:
    a. Indicated
    b. Strongly indicated
    c. Compulsory procedure
    d. Contraindicated

Correct answers: 1d, 2d, 3d, 4a, 5d

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THEME 2

LIP CANCER. CANCER OF THE ORAL CAVITY

2.1. EPIDEMIOLOGY

The estimated number of new head and neck cancer cases (excluding skin cancer) in the United States in 2009 was 48,010; this represents 3.2 % of the total new cancer cases. Approximately 7 % of these patients are women. African Americans have a higher age-adjusted incidence than other ethnic groups. The usual time of diagnosis is after the age of 40, except for salivary gland and nasopharyngeal cancers (NPCs), which may occur in younger age groups. For many primary sites, tobacco use is associated with an increased risk. Alcohol has also been implicated as a causative factor; the effects of alcohol and tobacco may be synergistic. Head and neck cancer patients have an increased risk for developing a second primary tumor (SPT) , both within the head and neck and elsewhere (e.g., esophageal and lung cancers), attributed to the field defect associated with tobacco and alcohol use. Human papillomavirus infection (HPV; most commonly HPV-16) plays a role in the development of certain head and neck cancers, particularly those in the oropharynx. Patients with high-risk HPV (HR-HPV) positive head and neck cancers tend to be younger and less likely to have a strong history of tobacco and ethanol use, have a history of multiple sex partners (particularly oralgenital sex), and have a better prognosis. There is a longstanding association between Epstein-Barr virus (EBV) and NPC. Occupational exposures are associated with the development of sinonasal tract tumors.

2.2. ANATOMY

The anatomy pertaining to a particular primary site is described in subsequent sections. To facilitate communication, lymph nodes are organized into levels. Level I includes the submental and submandibular areas; levels II-IV include the internal jugular vein lymph nodes; level V includes the posterior triangle. Furthermore, which lymph node levels are involved are predictive of the primary site. For example, lip, oral cavity, and facial skin tumors typically spread to level I initially; larynx and pharynx cancers have a predilection for spread to levels II and III.

There are no capillary lymphatics in the epithelium. Tumor must penetrate the lamina propria before lymphatic invasion can occur. One can predict the richness of the capillary network in a given head and neck site by the relative incidence of lymph node metastases at presentation. The nasopharynx and pyriform sinus have the most profuse capillary lymphatic networks. The paranasal sinuses, middle ear, and vocal cords have few or no capillary lymphatics. Muscle and fat contain few capillary lymphatics, as do bone and cartilage within the periosteum or perichondrium. There are no capillary lymphatics in the eye, and few in the orbit.

2.3. PATHOLOGY

Most head and neck malignant neoplasms arise from the surface epithelium and are squamous cell carcinoma (SCC) or one of its variants, including lymphoepithelioma, spindle cell carcinoma, verrucous carcinoma, and undifferentiated carcinoma.

Lymphomas and a wide variety of other malignant and benign neoplasms make up the remaining cases. Lymphoepithelioma is an SCC with a lymphoid stroma and occurs in the nasopharynx, tonsillar fossa, and base of tongue; it may also occur in the salivary glands. In the spindle cell variant, found in 2% to 5% of upper aerodigestive tract malignancies, there is a spindle cell component that resembles sarcoma intermixed with sec. It is generally managed like other high-grade SCCs. Verrucous carcinoma is a low-grade SCC found most often in the oral cavity, particularly on the gingiva and buccal mucosa. It usually has an indolent growth pattern and is often associated with the chronic use of snuff or chewing tobacco.

2.4. DIAGNOSIS

A general medical evaluation is performed, including a thorough head and neck examination. The location and extent of the primary tumor and any clinically positive lymph nodes is documented. Almost all patients undergo contrast enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) to further define the extent of locoregional disease. The authors prefer to use CT and reserve MRI for situations in which further information is required. The scan(s) should be obtained prior to biopsy so that biopsy changes are not confused with tumor. A chest radiograph is obtained to determine the presence of distant metastases and/or a synchronous primary lung cancer. Patients with N3 neck disease, as well as those with N2 disease with nodes below the level of the thyroid notch, have a 20% to 30% risk of developing distant metastases and are considered for a chest CT or positron emission tomography (PET).

Tumors amenable to transoral biopsy may be biopsied using local anesthetics in the clinic. Otherwise direct laryngoscopy under anesthesia is performed to determine the extent of the tumor and to obtain a tissue diagnosis. Given the risk of synchronous ancers, some advocate routine triple endoscopy (i.e., laryngoscopy/pharyngoscopy, bronchoscopy, and esophagoscopy). The additional yield is low, unless diffuse mucosal abnormalities or a malignant lymph node without an identified primary site, particularly in the low neck, are present. Patients presenting with a metastatic node from an unknown primary site undergo fine-needle aspiration (FNA) of the node. Excisional biopsy is not routinely performed unless lymphoma is suspected or FNA results are equivocal. If SCC is a consideration, the excision should be done in a manner to facilitate subsequent management, including neck dissection.

Occasionally the diagnosis may be made by clinical and radiographic evaluation, and biopsy is avoided in situations in which the treatment is definitive RT and obtaining tissue is risky (i.e., paragangliomas or juvenile nasopharyngeal angiofibromas).

Before initial treatment, the patient should be evaluated by members of the team who may be involved in the initial management as well as possible salvage therapy. Head and neck surgeons, radiation oncologists, medical oncologists, diagnostic radiologists, plastic surgeons, pathologists, dentists, speech and swallowing therapists, and social workers may all play a role. The treatment options are discussed and recommendations are presented to the patient who makes the final decision.

2.5. TNM-CLASSIFICATION

Primary Tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ
T1 Tumour 2 cm or less in greatest dimension
T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension
T3 Tumour more than 4 cm in greatest dimension
T4a *(lip)* Tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)
T4a *(oral cavity)* Tumour invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b *(lip and oral cavity)* Tumour invades masticator space, pterygoid plates, or skull base, or encases internal carotid artery

Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumour as T4.

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2 Metastasis as described below:
N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension
Note: Midline nodes are considered ipsilateral nodes.

M – Distant Metastasis
M0 No distant metastasis
M1 Distant metastasis

Grouping for stages

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVa	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVb	Any T	N3	M0
	T4b	Any N	M0
IVc	Any T	Any N	M1

2.6. TREATMENT

Depending on the site and extent of the primary tumor and the status of the lymph nodes, some general considerations for the treatment of lip and oral cavity cancer include the following:

- Surgery alone.
- Radiation therapy alone.
- A combination of the above.

For lesions of the oral cavity, surgery must adequately encompass all of the gross as well as the presumed microscopic extent of the disease. If regional nodes are positive, cervical node dissection is usually done in continuity. With modern approaches, the surgeon can successfully ablate large posterior oral cavity tumors and with reconstructive methods can achieve satisfactory functional results. Prosthodontic rehabilitation is important, particularly in early-stage cancers, to assure the best quality of life.

THEME 2: LIP CANCER. CANCER OF THE ORAL CAVITY

Radiation therapy for lip and oral cavity cancers can be administered by external-beam radiation therapy (EBRT) or interstitial implantation alone, but for many sites the use of both modalities produces better control and functional results. Small superficial cancers can be very successfully treated by local implantation using any one of several radioactive sources, by intraoral cone radiation therapy, or by electrons. Larger lesions are frequently managed using EBRT to include the primary site and regional lymph nodes, even if they are not clinically involved. Supplementation with interstitial radiation sources may be necessary to achieve adequate doses to large primary tumors and/or bulky nodal metastases. A review of published clinical results of radical radiation therapy for head and neck cancer suggests a significant loss of local control when the administration of radiation therapy was prolonged; therefore, lengthening of standard treatment schedules should be avoided whenever possible.

Early cancers (stage I and stage II) of the lip, floor of the mouth, and retromolartrigone are highly curable by surgery or radiation therapy. The choice of treatment is dictated by the anticipated functional and cosmetic results. Availability of the particular expertise required of the surgeon or radiation oncologist for the individual patient is also a factor in treatment choice.

Advanced cancers (stage III and stage IV) of the lip, floor of the mouth, and retromolartrigone represent a wide spectrum of challenges for the surgeon and radiation oncologists. Most patients with stage III or stage IV tumors are candidates for treatment by a combination of surgery and radiation therapy. Patients with small T3 lesions and no regional lymph nodes, and no distant metastases or patients who have no lymph nodes larger than 2 cm in diameter, for whom treatment by radiation therapy alone or surgery alone might be appropriate, are the exceptions.

The potential role of radiation modifiers to improve local control or decrease morbidity.

The role of combinations of chemotherapy with surgery and/or radiation therapy both to improve local control and to decrease the frequency of distant metastases.

Early cancers of the buccal mucosa are equally curable by radiation therapy or by adequate excision. Patient factors and local expertise influence the choice of treatment. Larger cancers require composite resection with reconstruction of the defect by pedicle flaps.

Early lesions (T1 and T2) of the anterior tongue may be managed by surgery or by radiation therapy alone. Both modalities produce 70% to 85% cure rates in early lesions. Moderate excisions of tongue, even hemiglossectomy, can often result in little speech disability provided the wound closure is such that the tongue is not bound down. If, however, the resection is more extensive, problems may include aspiration of liquids and solids and difficulty in swallowing in addition to speech difficulties. Occasionally, patients with tumor of the tongue require almost total glossectomy. Large lesions generally require combined surgical and radiation treatment. The control rates for larger lesions are about 30% to 40%.

THEME 2: LIP CANCER. CANCER OF THE ORAL CAVITY

According to clinical and radiological evidence of involvement, cancers of the lower gingiva that are exophytic and amenable to adequate local excision may be excised to include portions of bone. More advanced lesions require segmental bone resection, hemimandibulectomy, or maxillectomy, depending on the extent of the lesion and its location.

Early lesions of the upper gingiva or hard palate without bone involvement can be treated with equal effectiveness by surgery or by radiation therapy alone. Advanced infiltrative and ulcerating lesions should be treated by a combination of radiation therapy and surgery. Most primary cancers of the hard palate are of minor salivary gland origin. Primary squamous cell carcinoma of the hard palate is uncommon, and these tumors generally represent invasion of squamous cell carcinoma arising on the upper gingiva, which is much more common. Management of squamous cell carcinoma of the upper gingiva and hard palate are usually considered together. Surgical treatment of cancer of the hard palate usually requires excision of underlying bone producing an opening into the antrum. This defect can be filled and covered with a dental prosthesis, which is a maneuver that restores satisfactory swallowing and speech.

Patients who smoke while on radiation therapy appear to have lower response rates and shorter survival durations than those who do not; therefore, patients should be counseled to stop smoking before beginning radiation therapy. Dental status evaluation should be performed prior to therapy to prevent late sequelae.

Stage I Lip and Oral Cavity Cancer

Surgery and/or radiation therapy may be used, depending on the exact site.

Small Lesions of the Lip

Standard treatment options:

- Surgery.
- Radiation therapy.

Surgery and radiation therapy produce similar cure rates, and the method of treatment is dictated by the anticipated cosmetic and functional results.

Small Anterior Tongue Lesions

Standard treatment options:

1. Wide local excision is often used for small lesions that can be resected transorally.
2. For patients with larger T1 lesions, the following standard treatments are used:
    a. Surgery.
    b. Radiation therapy.
    c. Interstitial implantation alone or with external-beam radiation therapy.
    d. Irradiation of the neck.

Small Lesions of the Buccal Mucosa
Standard treatment options:

1. Surgery alone for patients with lesions smaller than 1 cm in diameter, if the commissure is not involved.
2. Radiation therapy, including brachytherapy, should be considered to treat lesions smaller than 1 cm in diameter, if the commissure is involved.
3. Surgical excision with a split-thickness skin graft or radiation therapy is used to treat larger T1 lesions.

Small Lesions of the Floor of the Mouth
Standard treatment options:

1. Surgery for patients with T1 lesions.
2. Radiation therapy is used to treat T1 lesions.
3. Excision alone is generally adequate to treat lesions smaller than 0.5 cm, if there is a margin of normal mucosa between the lesion and the gingiva.
4. Surgery is often used, if the lesion is attached to the periosteum.
5. Radiation therapy is often used, if the lesion encroaches on the tongue.

Small Lesions of the Lower Gingiva
Standard treatment options:

1. Intraoral resection with or without a rim resection of bone and repair with a split-thickness skin graft are used to treat small lesions.
2. Radiation therapy may be used for small lesions, but results are generally better after surgery alone.

Small Tumors of the RetromolarTrigone
Standard treatment options:

1. Limited resection of the mandible is performed for early lesions without detectable bone invasion.
2. Radiation therapy may be used initially, if limited resection is not feasible, with surgery reserved for radiation failure.

Small Lesions of the Upper Gingiva and Hard Palate
Standard treatment options:

1. Surgical resection is used to treat most small lesions.
2. Postoperative radiation therapy may be used, if appropriate.

<u>Stage II Lip and Oral Cavity Cancer</u>
Surgery and/or radiation therapy may be used, depending on the exact site.

Small Lesions of the Lip
Standard treatment options:

1. Surgery is used for patients with smaller T2 lesions on the lower lip, if simple closure produces an acceptable cosmetic result.
2. Radiation therapy, which may include external-beam and/or interstitial techniques, as appropriate, has the advantage of producing a relatively better functional and cosmetic result with intact skin and muscle innervation, if a reconstructive surgical procedure is required.

Small Anterior Tongue Lesions
Standard treatment options:

1. Radiation therapy is usually selected for patients with T2 lesions that have minimal infiltration to preserve speech and swallowing.
2. Surgery is reserved for patients for whom radiation treatment failed.
3. Neck dissection may be considered when primary brachytherapy is used.
4. Surgery, radiation therapy, or a combination of both are used for deeply infiltrative lesions.

Small Lesions of the Buccal Mucosa
Standard treatment options:

1. Radiation therapy is the usual treatment for patients with small T2 lesions (≤3 cm).
2. Surgery, radiation therapy, or a combination of these are used, if indicated to treat large T2 lesions (>3 cm). Radiation therapy is often used, if the lesion involves the commissure. Surgery is often used, if tumor invades the mandible or maxilla.

Small Lesions of the Floor of the Mouth
Standard treatment options:

1. Surgery is often used for patients with small T2 lesions (≤3 cm), if the lesion is attached to the periosteum.
2. Radiation therapy is often used to treat patients with small T2 lesions (≤3 cm), if the lesion encroaches on the tongue.
3. Surgery and radiation therapy are alternative methods of treatment for patients with large T2 lesions (>3 cm), the choice of which depends primarily on the expected extent of disability from surgery.
4. External-beam radiation therapy with or without interstitial radiation therapy should be considered postoperatively for larger lesions.

Small Lesions of the Lower Gingiva
Standard treatment options:

1. Intraoral resection with or without a rim resection of bone and repair with a split-thickness skin graft are used to treat patients with small lesions.
2. Radiation therapy may be used to treat patients with small lesions, but results are generally better after surgery alone.

Small Tumors of the RetromolarTrigone
Standard treatment options:

1. Limited resection of the mandible is performed to treat patients with early lesions that are without detectable bone invasion.
2. Radiation therapy may be used initially, if limited resection is not feasible.
3. Surgery is reserved for radiation failure.

Small Lesions of the Upper Gingiva and Hard Palate
Standard treatment options:
Surgical resection with postoperative radiation therapy, as appropriate, is used to treat most lesions. A small study showed that radiation therapy may be used effectively as the sole treatment modality.

Stage III Lip and Oral Cavity Cancer

Surgery and/or radiation therapy are used, depending on the exact tumor site.Neoadjuvant chemotherapy, as given in clinical trials, has been used to shrink tumors and render them more definitively treatable with either surgery or radiation. Neoadjuvant chemotherapy is given prior to the other modalities, as opposed to standard adjuvant chemotherapy, which is given after or during definitive therapy with radiation or after surgery. Many drug combinations have been used as neoadjuvant chemotherapy. Randomized, prospective trials, however, have yet to demonstrate a benefit in either disease-free survival or overall survival for patients receiving neoadjuvant chemotherapy.

Advanced Lesions of the Lip
These lesions, including those involving bone, nerves, and lymph nodes, generally require a combination of surgery and radiation therapy.

Standard treatment options:

1. Surgery using a variety of surgical approaches, the choice of which is dependent on the size and location of the lesion and the needs for reconstruction.
2. Radiation therapy using a variety of therapy techniques, including external-beam radiation therapy (EBRT) with or without brachytherapy, the choice of which is dictated by the size and location of the lesion.

Treatment options under clinical evaluation:

1. Clinical trials for advanced tumors evaluating the use of chemotherapy preoperatively, before radiation therapy, as adjuvant therapy after surgery, or as part of combined modality therapy are appropriate.
2. Superfractionated radiation therapy.

Moderately Advanced (Late T2, Small T3) Lesions of the Anterior Tongue
Standard treatment options:

1. EBRT with or without interstitial implant is used to treat minimally infiltrative lesions.
2. Surgery with postoperative radiation therapy is used to treat deeply infiltrative lesions.

Advanced Lesions of the Buccal Mucosa
Standard treatment options:

1. Radical surgical resection alone.
2. Radiation therapy alone.
3. Surgical resection plus radiation therapy, generally postoperative.

Treatment options under clinical evaluation:

- Clinical trials for advanced tumors evaluating the use of chemotherapy preoperatively, before radiation therapy, as adjuvant therapy after surgery, or as part of combined modality therapy are appropriate.

Moderately Advanced Lesions of the Floor of the Mouth
Standard treatment options:

1. Surgery using rim resection plus neck dissection or partial mandibulectomy with neck dissection, as appropriate.
2. Radiation therapy using EBRT alone or EBRT plus an interstitial implant.

Treatment options under clinical evaluation:

1. Clinical trials for advanced tumors evaluating the use of chemotherapy preoperatively, before radiation therapy, as adjuvant therapy after surgery, or as part of combined modality therapy are appropriate.
2. Clinical trials using novel radiation therapy fractionation schemas.

Moderately Advanced Lesions of the Lower Gingiva
Standard treatment options:

- Combined radiation therapy and radical resection or radical resection alone are used to treat extensive lesions with moderate bone destruction and/or nodal metastases; radiation therapy may be administered either preoperatively or postoperatively.

Advanced Lesions of the RetromolarTrigone
Standard treatment options:

- Surgical composite resection that may be followed by postoperative radiation therapy.

Treatment options under clinical evaluation:

1. Clinical trials for advanced tumors evaluating the use of chemotherapy preoperatively, before radiation therapy, as adjuvant therapy after surgery, or as part of combined modality therapy are appropriate.
2. Clinical trials using novel radiation therapy fractionation schemas.

Moderately Advanced Lesions of the Upper Gingiva
Standard treatment options:

1. Radiation therapy alone is used to treat superficial lesions with extensive involvement of the gingiva, hard palate, or soft palate.
2. A combination of surgery and radiation therapy is used to treat deeply invasive lesions involving bone.

Moderately Advanced Lesions of the Hard Palate
Standard treatment options:

1. Radiation therapy alone is used to treat superficial lesions with extensive involvement of the gingiva, hard palate, or soft palate.
2. A combination of surgery and radiation therapy or surgery alone is used to treat deeply invasive lesions involving bone.

Treatment options for management of lymph nodes:

- Patients with advanced lesions should have elective lymph node radiation therapy or node dissection. The risk of metastases to lymph nodes is increased by high-grade histology, large lesions, spread to involve the wet mucosa of the lip or the buccal mucosa in patients with recurrent disease, and invasion of muscle (i.e., orbicularis oris).

Standard treatment options:

1. Radiation therapy alone or neck dissection:
    a. N1 (0–2 cm).
    b. N2b or N3; all nodes smaller than 2 cm. (A combined surgical and radiation therapy approach should also be considered.)
2. Radiation therapy and neck dissection:
    a. N1 (2–3 cm), N2a, N3.
3. Surgery followed by radiation therapy, indications for which are as follows:
    a. Multiple positive nodes.
    b. Contralateral subclinical metastases.
    c. Invasion of tumor through the capsule of the lymph node.

   d. N2b or N3 (one or more nodes in each side of the neck, as appropriate, >2 cm).
4. Radiation therapy prior to surgery:
   a. Large fixed nodes.

Treatment options under clinical evaluation (all stage III lesions):

- Chemotherapy has been combined with radiation therapy in patients who have locally advanced disease that is surgically unresectable.

A meta-analysis of 63 randomized, prospective trials published between 1965 and 1993 showed an 8% absolute survival advantage in the subset of patients receiving concomitant chemotherapy and radiation therapy. Patients receiving adjuvant or neoadjuvant chemotherapy had no survival advantage. Cost, quality of life, and morbidity data were not available; no standard regimen existed; and the trials were felt to be too heterogenous to provide definitive recommendations. The results of 18 ongoing trials may further clarify the role of concomitant chemotherapy and radiation therapy in the management of oral cavity cancer.
The best chemotherapy to use and the appropriate way to integrate the two modalities is still unresolved.
Similar approaches in the patient with resectable disease, in whom resection would lead to a major functional deficit, are also being explored in randomized trials but cannot be recommended at this time as standard.
Novel fractionation radiation therapy clinical trials are under clinical evaluation.

<u>Stage IV Lip and Oral Cavity Cancer</u>
Randomized, prospective trials have yet to demonstrate a benefit in either disease-free survival or overall survival for patients receiving neoadjuvant chemotherapy. The use of isotretinoin (13-cis-retinoic acid) daily for 1 year to prevent development of second upper aerodigestive tract primaries is under clinical evaluation.

Advanced Lesions of the Lip
These lesions, including those involving bone, nerves, and lymph nodes, generally require a combination of surgery and radiation therapy.
Standard treatment options:

1. Surgery using a variety of surgical approaches, the choice of which is dependent on the size and location of the lesion and the needs for reconstruction. Treatment of both sides of the neck is indicated for selected patients.
2. Radiation therapy using a variety of therapy techniques, including external-beam radiation therapy (EBRT) with or without brachytherapy, the choice of which is dictated by the size and location of the lesion.

Treatment option under clinical evaluation:

- Superfractionated radiation therapy.

Advanced Lesions of the Anterior Tongue
Standard treatment options:

1. Combined surgery (i.e., total glossectomy, sometimes requiring laryngectomy) possibly followed by postoperative radiation therapy may be used to treat selected patients.
2. Palliative radiation therapy may be used to treat patients with very advanced lesions.

Advanced Lesions of the Buccal Mucosa
Standard treatment options:

1. Radical surgical resection alone.
2. Radiation therapy alone.
3. Surgical resection plus radiation therapy, which is generally administered postoperatively.

Advanced Lesions of the Floor of the Mouth
Standard treatment options:

1. A combination of surgery and radiation therapy, which is generally administered postoperatively, is often used.
2. Preoperative radiation therapy is often used for fixed nodes (≥5 cm).

Advanced Lesions of the Lower Gingiva
Standard treatment options:

- Surgery, radiation therapy, or a combination of both are poor controls for far advanced tumors with extensive destruction of the mandible and with nodal metastases.

Advanced Lesions of the RetromolarTrigone
Standard treatment options:

- Surgical composite resection followed by postoperative radiation therapy.

Advanced Lesions of the Upper Gingiva
Standard treatment options:

- Surgery in combination with radiation therapy is generally used to treat lesions that are extensive and infiltrating.

Advanced Lesions of the Hard Palate
Standard treatment options:

- Surgery in combination with radiation therapy is generally used to treat lesions that are extensive and infiltrating.

Treatment options for management of lymph nodes:

- Patients with advanced lesions should have elective lymph node radiation therapy or node dissection. The risk of metastases to lymph nodes is increased by high-grade histology, large lesions, spread involving the wet mucosa of the lip or the buccal mucosa in patients with recurrent disease, and invasion of muscle (orbicularis oris).

Standard treatment options:

1. Radiation therapy alone or neck dissection:
    a. N1 (0–2 cm).
    b. N2b or N3; all nodes smaller than 2 cm. (A combined surgical and radiation therapy approach should also be considered.)
2. Radiation therapy and neck dissection:
    a. N1 (2–3 cm), N2a, N3.
3. Surgery followed by radiation therapy is indicated for the following:
    a. Multiple positive nodes.
    b. Contralateral subclinical metastases.
    c. Invasion of tumor through the capsule of the lymph node.
    d. N2b or N3 (one or more nodes in each side of the neck, as appropriate, >2 cm).
4. Radiation therapy prior to surgery:
    a. Large fixed nodes.

Treatment options under clinical evaluation (all stage IV lesions):

1. Chemotherapy has been combined with radiation therapy in patients who have locally advanced disease that is surgically unresectable.A meta-analysis of 63 randomized, prospective trials published between 1965 and 1993 showed an 8% absolute survival advantage in the subset of patients receiving concomitant chemotherapy and radiation therapy. Patients receiving adjuvant or neoadjuvant chemotherapy had no survival advantage. Cost, quality of life, and morbidity data were not available; no standard regimen existed; and the trials were felt to be too heterogenous to provide definitive recommendations. The results of 18 ongoing trials may further clarify the role of concomitant chemotherapy and radiation therapy in the management of oral cavity cancer. The best chemotherapy to use and the appropriate way to integrate the two modalities is still unresolved. Similar approaches in the patient with resectable disease, in whom resection would lead to a major functional deficit,

are also being explored in randomized trials but cannot be recommended at this time as standard.
2. Clinical trials for advanced tumors evaluating the use of chemotherapy preoperatively, before radiation therapy, or as adjuvant therapy after surgery are appropriate.
3. Novel fractionation radiation therapy clinical trials are under clinical evaluation.

Recurrent Lip and Oral Cavity Cancer

For lesions of the lip, anterior tongue, buccal mucosa, floor of the mouth, retromolartrigone, upper gingiva, and hard palate, treatment will be dictated by the location and size of the recurrent lesion as well as prior treatment.

Standard treatment options:

1. Surgery is the preferred treatment, if radiation therapy was used initially.
2. Surgery, radiation therapy, or a combination of these may be considered for treatment, if surgery was used to treat the lesion initially.
3. Although chemotherapy has been shown to induce responses, no increase in survival has been demonstrated.

Treatment options under clinical evaluation:

- Clinical trials evaluating new chemotherapy drugs, chemotherapy and re-irradiation, or hyperthermia should be considered because surgical salvage after primary treatment by radiation therapy and radiation therapy after primary surgery give poor results.

2.7. QUESTIONS FOR SELF-CONTROL

1. What histological type of malignancies is in patients wit oral cavity cancer more frequently?
2. What are the causes of oral cavity malignancies?
3. What is leukoplakia and erythroplakia?
4. How is cervical lymph node assessment performed?
5. How is an oral cavity cancer diagnosed and confirmed?

2.8. TESTS FOR SELF-CONTROL

1. Approximately 90% of all oral cancers are:
    a. Basal cell cancer
    b. Squamous cell carcinoma
    c. Adenocarcinoma
    d. Mucoepidermoidal cancer

2. What is the most common risk factor of oral cavity cancer?
    a. Ionizing irradiation exposure
    b. Cigarette smoking
    c. Acromegaly and Barrett`s esophagus
    d. None of the above
3. Immune deficient conditions may predispose cancer of the:
    a. Tongue
    b. Mouth
    c. Tongue and mouth
    d. Lip
4. The most common site for oral cancers is:
    a. Lower lip and lateral margin of tongue
    b. Upper lip and lateral margin of tongue
    c. Distal margin of tongue
    d. Tongue
5. The diagnosis of oral cancer must be confirmed:
    a. By X-Ray of the head
    b. By CT scan of the head
    c. By stomatoscopy
    d. By biopsy

Correct answers: 1b, 2b, 3d, 4a, 5d

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THEME 3

BREAST CANCER

3.1. EPIDEMIOLOGY

Breast cancer is a major public health problem for women throughout the world. In the United States, breast cancer remains the most frequent cancer in women and the second most frequent cause of cancer death. In 2009 it is estimated that breast cancer accounted for 27% of cancer cases and 15% of cancer deaths, which translates to 192370 new cases and 40170 deaths. Breast cancer was also the most common form of cancer seen in Europe in 2006, with 429900 new cases, representing 13.5 % of all new cancers. Since 1 990, the death rate from breast cancer has decreased in the United States by 24 % and similar reductions have been observed in other countries. Mathematical models suggest that both the adoption of screening mammography and the availability of adjuvant chemotherapy and tamoxifen have contributed approximately equally to this improvement. Although breast cancer has traditionally been less common in nonindustrialized nations, its incidence in these areas is increasing. Industrialization in developing countries is associated with rapid increases in breast cancer risk.

3.2. ETIOLOGY, RISK FACTORS

Multiple factors are associated with an increased risk of developing breast cancer, including increasing age, family history exposure to female reproductive hormones (both endogenous and exogenous) , dietary factors, benign breast disease, reproductive history, and environmental factors. The maj ority of these factors convey a small to moderate increase in risk for any individual woman. It has been estimated that approximately 50% of women who develop breast cancer have no identifiable risk factor beyond increasing age and female gender.

The importance of age as a breast cancer risk factor is sometimes overlooked. In 2009 it was estimated that 18,640 invasive breast cancers and 2,820 breast cancer deaths occurred in U.S. women under age 45 compared with 173,730 cancers and 37,350 deaths in women aged 45 years and older.

Familial Factors

A family history of breast cancer has long been recognized as a risk factor for the disease. The majority of women diagnosed with breast cancer do not have a family member with the disease, and only 5% to 10% have a true hereditary predisposition to breast cancer. Many women with a positive family history overestimate their risk of developing breast cancer, and women considering genetic testing have been shown to overestimate their chance of having a mutation. Overall, the risk of developing breast cancer is increased 1.5-fold to threefold if a woman has a mother or sister with breast cancer.

Family history, however, is a heterogeneous risk factor with different implications depending on the number of relatives with breast cancer, the exact relationship, the age at diagnosis, and the number of unaffected relatives. For example, there may be a minimal elevation in breast cancer risk for a woman whose mother was diagnosed with breast cancer at an advanced age and who has no other family history of the disease. In contrast, a woman who has multiple family members diagnosed with early-onset breast cancer is at a much higher risk of developing the disease. Even in the absence of a known inherited predisposition, women with a family history of breast cancer face some level of increased risk, likely from some combination of shared environmental exposures, unexplained genetic factors, or both.

Inherited Predisposition to Breast Cancer

Mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 are associated with a significant increase in the risk of breast and ovarian carcinoma and account for 5% to 10% of all breast cancers. These mutations are inherited in an autosomal dominant fashion and have varying penetrance. As a result, the estimated lifetime risk of breast cancer development in mutation carriers ranges from 26% to 85% , and the risk of ovarian cancer from 16% to 63% and 10% to 27%, respectively, in carriers of BRCA1 and BRCA2. More than 700 different mutations of BRCA1 and 300 different mutations of BRCA2 have been described, and the position of the mutation within the gene has been shown to influence the risk of both breast and ovarian cancers, with an increased risk of ovarian carcinoma among BRCA1 carriers with mutations in the two-thirds o f the gene and a n increased risk of ovarian carcinoma among BRCA2 carriers with mutations between nucleotides 4075-6503.

Other cancers associated with BRCA1 or BRCA2 mutations include male breast cancer, fallopian tube cancer, and prostate cancer. Carriers of BRCA2 may also have an elevated risk of melanoma and gastric cancer. Management strategies available for risk reduction in BRCA1/2 mutation carriers include intensive surveillance, chemoprevention with selective estrogen receptor modulators (SERMs), and prophylactic (breast and salpino-ovarian) surgery, and these are discussed in a later section. There is a great interest in the role of environmental and lifestyle factors in the modification of cancer risk among BRCA1 or BRCA2 carriers; at present, however, the available data are inconsistent. It is worth noting that women with a significant family history of breast cancer (i.e., two or more breast cancers under the age of 50 years, or three or more breast cancers at any age), but who test negative for BRCA mutations have approximately a fourfold risk of breast cancer and that women in these families may be candidates for tamoxifen chemoprevention and/or intensified breast screening.

The histologic features of cancers arising in women with BRCA1 mutations differ from those occurring sporadically, with a higher incidence of medullary features and a higher proportion of grade 3 tumors.

The proportion of BRCA1 cancers expressing the estrogen receptor (ER) or progesterone receptor (PR) is lower than is seen in sporadic cancers, and HER2 overexpression is infrequent. This triple-negative pattern is consistent with the basal cell phenotype. In contrast, it is not clear that the phenotype of BRCA2 cancers differs from that seen in sporadic cancers, although some studies have suggested an excess of tubular and lobular carcinomas.

The presence of a BRCA 1 or BRCA2 mutation may be suggested by the family history on either the maternal or paternal side of the family. Less rigorous criteria for referral for genetic counseling are used for individuals of Ashkenazi Jewish ancestry because the carrier frequency of specific BRCA1 and BRCA2 mutations in this group is 1:40 compared with 1:500 in the general population. These guidelines are particularly useful for individuals not affected with breast cancer.

In the newly diagnosed breast cancer patient, young age at diagnosis (40 years or less) , bilateral breast cancer, Ashkenazi ancestry, or a malignancy consistent with the BRCA 1 phenotype
all constitute reasons for referral to a genetic counselor, particularly in the woman with a small number of female relatives. Genetic testing should be preceded by a careful evaluation of an individual's personal cancer history and family history.

Models are available to estimate the likelihood of a BRCA1 or BRCA2 mutation based on family history. The implications of genetic testing for both individuals and their family members are considerable, and these issues should be discussed prior to undertaking genetic testing.

Hormonal Factors

The development of breast cancer in many women appears to be related to female reproductive hormones. Epidemiologic studies have consistently identified a number of breast cancer risk factors associated with increased exposure to endogenous estrogens . Early age at menarche, nulliparity or late age at first full-term pregnancy, and late age at menopause increase the risk of developing breast cancer. In postmenopausal women, obesity and postmenopausal hormone replacement therapy (HRT), both of which are positively correlated with plasma estrogen levels and plasma estradiol levels, are associated with increased breast cancer risk. Furthermore, in utero exposure to high concentrations of estrogen may also increase breast cancer risk. Most hormonal risk factors have a relative risk of 2.0 or less for breast cancer development.

The age-specific incidence of breast cancer increases steeply with age until menopause. After menopause, although the incidence continues to increase, the rate of increase decreases to approximately one-sixth of that seen in the premenopausal period. The dramatic slowing of the rate of increase in the agespecific incidence curve suggests that ovarian activity plays a maj or role in the etiology of breast cancer. There is substantial evidence that estrogen deprivation via iatrogenic premature menopause can reduce breast cancer risk.

Epidemiologic studies have shown that premenopausal women who undergo oophorectomy without hormone replacement have a markedly reduced risk of breast cancer later in life. Oophorectomy before age 50 decreases breast cancer risk, with an increasing magnitude of risk reduction as the age at oophorectomy decreases. Data from women with BRCA 1 and BRCA2 mutations suggest that early oophorectomy has a substantial protective effect on breast cancer risk in this population as well.

Age at menarche and the establishment of regular ovulatory cycles are strongly linked to breast cancer risk. Earlier age at menarche is associated with an increased risk of breast cancer; there appears to be a 20% decrease in breast cancer risk for each year that menarche is delayed. Of note, hormone levels through the reproductive years in women who experience early menarche may be higher than in women who undergo a later menarche. Additionally, late onset of menarche results in a delay in the establishment of regular ovulatory cycles, although there is some controversy over whether this delay confers any additional protective effect. From these data regarding menarche and menopause, it seems likely that the total duration of exposure to endogenous estrogen is an important factor in breast cancer risk.

3.3. DIAGNOSIS

The presence or absence of carcinoma in a suspicious clinically or mammographically detected abnormality can only be reliably determined by tissue sampling. The high sensitivity of MRI for cancer detection raised the possibility that this technique could replace biopsy in the evaluation of suspicious breast lesions. In a multi-institutional prospective study of 821 patients referred for breast biopsy, the sensitivity of MRI was 88.1% (95% CI, 84.6%-91.1%) and the specificity was 67.7% (95% CI, 62.7%-71.9 %), indicating that an abnormal MRI does not reliably indicate the presence of cancer, and a nonworrisome MRI does not reliably exclude carcinoma.

A biopsy remains the standard technique for diagnosing both palpable and nonpalpable breast abnormalities . The available biopsy techniques for the diagnosis of palpable breast masses are fine-needle aspiration (FNA), core-cutting needle biopsy, and excisional biopsy. Both FNA and core biopsy are office procedures. FNA is easily performed, but requires a trained cytopathologist for accurate specimen interpretation. The sensitivity of FNA ranges from 80% to 95%, and false-positive aspirates are seen in less than 1% of cases in most series. False-negative results are seen in 4% to 10% of cases and are most common in fibrotic or well-differentiated tumors.

Although an FNA diagnosis of malignant cells is sufficient to proceed with definitive treatment, FNA does not reliably distinguish invasive leading to the overtreatment of gross DCIS.

Core-cutting needle biopsy has many of the advantages of FNA, but provides a histologic specimen suitable for interpretation by any pathologist. In addition, ER and PR status and the presence of HER2 overexpression can be routinely determined from core biopsy specimens, making core needle biopsy the diagnostic technique of choice for patients who will receive preoperative systemic therapy. False-negative results from sampling error may also occur with core-cutting needle biopsy.

If concordance between the core biopsy diagnosis and the clinical and imaging findings is not present, additional tissue should be obtained, usually by excisional biopsy. When excisional biopsy is performed for diagnosis, a small margin of grossly normal breast should be excised around the tumor, orienting sutures should be placed, and the specimen should be inked to allow margin evaluation. This procedure allows an assessment of the completeness of the excision if carcinoma is found, sparing patients with negative margins further breast surgery and allowing re-excision to be limited to the involved margin surface(s). However, diagnosis by needle biopsy is the preferred initial method of evaluating almost all breast masses. A needle biopsy diagnosis permits a complete discussion of treatment options prior to the placement of an incision on the breast and allows the breast procedure and the axillary surgery to take place at a single operation. In addition, needle biopsy is a more cost-effective method of diagnosing benign lesions than surgical excision.

Nonpalpable lesions can be biopsied with image-guided core needle biopsy or surgical excision after wire localization. Ultrasound guidance is used for lesions that are visualized with this modality; most calcifications require stereotactic mammographic guidance for biopsy. There is little role for FNA in the diagnosis of lesions detected by screening because of the high prevalence of in situ lesions. Concerns about the false-negative rate of image-guided core biopsy have been resolved with the availability of large, vacuum-assisted biopsy devices that increase the extent of lesion sampling, coupled with the development of clearly defined indications for follow-up surgical
biopsy. In a study of 318 patients with mammographic abnormalities diagnosed by core biopsy between September 1997 and December 2001, the false-negative rate was 3.3%. For radiologists who had done more than 15 biopsies, the falsenegative rate was 0.6% . All of the false negatives were recognized at the time, with no delay in the diagnosis of cancer. Although the finding of atypical ductal hyperplasia on a core biopsy is uniformly accepted as an indication for surgical biopsy, the need for surgical excision of all lesions showing atypical lobular hyperplasia or LCIS remains controversial Papillary carcinoma in situ cannot always be readily distinguished from benign papillary lesions on a core biopsy, and radial scar may be difficult to distinguish from tubular carcinoma without complete removal of the lesion.

The use of core biopsy for the diagnosis of mammographic abnormalities is cost-effective and increases the likelihood that the patient will be able to undergo a single surgical procedure for definitive cancer treatment.

In a prospective study of 1,550 consecutive patients undergoing biopsy for mammographic abnormalities, core biopsy reduced the number of surgical procedures needed for cancers presenting as both masses and calcifications as well as in patients requiring axillary staging and those treated by mastectomy. In a cost analysis using patients from this data set, core biopsy resulted in cost savings for all clinical scenarios. In spite of this, in a study of 5.5 million mammograms performed in two U.S. government-sponsored screening programs and the U.K. National Health Service etween 1996 and 1999, 51% of the biopsies performed in the United States were surgical, compared with 23 % in the United Kingdom.

3.4. LOBULAR CARCINOMA IN SITU

In 1941 Foote and Stewart published their landmark study of LCIS, describing a relatively uncommon entity characterized by an " alteration of lobular cytology." Foote and Stewart chose the name to emphasize the morphologic similarities between the cells of LCIS and those of invasive lobular carcinoma (ILC) . They hypothesized that LCIS represented a precursor lesion of invasive cancer, and, based on this, mastectomy was initially recommended. Subsequent studies, discussed later, have shown that the risk of subsequent breast cancer is bilateral. More recently, the term atypical lobular hyperplasia (ALH) has been introduced to describe morphologically similar, but less welldeveloped lesions. Some centers use the term lobular neoplasia (LN) to cover both ALH and LCIS. Morphologically, LN is defined as "a proliferation of generally small and often loosely cohesive cells originating in the terminal duct-lobular unit, with or without pagetoid involvement of terminal ducts.

In the past, LCIS was most frequently diagnosed in women aged 40 to 50, a decade earlier than DCIS, but recent literature indicates that the incidence in postmenopausal women is increasing. Determining the true incidence of LCIS is difficult as there are no specific clinical or mammographic abnormalities associated with the lesion. LCIS is typically not associated with microcalcifications on mammography. The diagnosis of LCIS is therefore often made as an incidental, microscopic finding in a breast biopsy performed for other indications. The prevalence of LN in an otherwise benign breast biopsy has been reported as between 0.5% and 4.3%. LCIS is both multifocal and bilateral in a large percentage of cases. In an analysis of nine separate studies evaluating outcome following a diagnosis of LCIS 172 patients who were treated by biopsy alone were identified. On follow-up averaging about 10 years, 15% of these patients had invasive carcinoma diagnosed in the ipsilateral breast and 9.3% had invasive carcinoma in the contralateral breast. This corresponds to an increased rate of development of invasive carcinoma of about 1 % to 2 % per year, with a lifetime risk of 30% to 40%. In this study (conducted prior to effective breast imaging), 5.7% of the patients developed metastatic breast cancer.

Subsequent cancers are more often invasive ductal carcinoma than ILC, but the incidence of subsequent ILC is substantially increased compared with women without LCIS. Although the risk for development of breast cancer
is bilateral, subsequent ipsilateral carcinoma is more likely than contralateral breast, supporting the view that ALH and LCIS act both as precursor lesions and as risk indicators. The relative risk for development of subsequent breast cancer is lower in women diagnosed with ALH compared with LCIS.

Therefore, although LN is a helpful term for collectively describing this group of lesions, specific classification into ALH and LCIS is preferable in terms of risk assessment and management. LCIS is typically positive for ER and PR staining by immunohistochemistry (IHC) and negative for HER2/neu staining. LN (and ILC) characteristically lacks expression of E-cadherin, an epithelial cell membrane molecule involved in cell-cell adhesion. E-cadherin negativity serves as a fairly reliable means of distinguishing ductal from lobular disease, both in situ and invasive. Pleomorphic LCIS is a relatively uncommon variant of LCIS characterized by medium to large pleomorphic cells containing eccentric nuclei, prominent nucleoli, and eosinophilic cytoplasm. As with classic LCIS, it is usually ER-positive and negative for E-cadherin; it also tests positive by IHC for gross cystic disease fluid protein. Pleomorphic LCIS can be associated with central necrosis and may be associated with mammographic microcalcifications. It is not clear at this time whether pleomorphic LCIS has a different natural history than classic LCIS .

Genetic changes in LN have been evaluated in a number of studies using comparative genomic hybridization. In one study ALH showed gain at 2p11.2 and loss at 7p11-p11.1 and 22q11.1, and LCIS showed gain a t 20q13.13 and loss at 19q13.2-q13.31.54 In both ALH and LCIS, there was loss at 16q21-q23.1, an altered region previously identified in invasive carcinoma. This genomic signature, common to LN and ILC, further suggests that LN is a precursor lesion in some women.

Management of LN must address the bilateral risk, and options therefore include surveillance, chemoprevention, and prophylactic bilateral mastectomy. Surveillance is the strategy
selected by most patients. Mammographic screening is the standard breast imaging for patients selecting surveillance. Breast MRI has been used, but there is no firm evidence supporting its efficacy; its value is being tested in a randomized clinical trial in Europe. Prophylactic mastectomy reduces breast cancer risk among high-risk women by approximately 90%. Chemoprevention with tamoxifen in patients with LCIS has been evaluated as part of the NSABPP1 study. In this prospective, placebo-controlled clinical trial, with a median follow-up of 54.6 months, tamoxifen reduced the incidence of breast cancer by 49% ($P<0.00001$). Eight hundred twenty-six of the participants had a history of LCIS, and breast cancers were detected in 1 8 women randomized to placebo and eight to tamoxifen, consistent with the overall reduction in breast cancer risk seen with tamoxifen. However, with the small number of events, this difference was not statistically significant.

In the NSABP P2 (STAR) trial comparing tamoxifen and raloxifene, comparable efficacy in risk reduction was observed. In this study, 893 participants gave a history of LCIS, and their rates of subsequent breast cancer were similar with tamoxifen and raloxifene. This benefit with tamoxifen or raloxifene needs to be weighed against the possible side effects of treatment.

Although the data are conflicting, it is generally recommended to perform an excisional biopsy after detection of LN on a core needle biopsy to rule out coexisting DCIS or invasive cancer. Some have advocated a more selective approach to LCIS on core biopsy based on whether or not there is concordance between the pathology and imaging findings. With LCIS, most reported cases of malignant findings on subsequent excision occur in the setting of either a suspicious mass lesion or calcifications that prompted the biopsy initially. The recent recognition that in some cases LCIS may be a precursor lesion has led to confusion as to whether it should be treated like DCIS (i.e., excised to negative margins and irradiated). At this time, there are no data indicating that the incidence of subsequent cancer is reduced with this approach. When LCIS is seen on an excised tissue, it is not necessary to obtain negative margins of resection, and there is no established role for radiation therapy in patients with LN.

3.5. DUCTAL CARCINOMA IN SITU

DCIS is defined as the proliferation of malignant-appearing mammary ductal epithelial cells without evidence of invasion beyond the basement membrane. Prior to the widespread use of screening mammography, fewer than 5% of mammary cancers were DCIS. At present 15% to 30% of the cancers detected in mammography screening programs are DCIS, and the greatest increase in the incidence of DCIS has been seen in women aged 49 to 69 years. DCIS can present as a palpable mass, Paget disease of the nipple, an incidental finding at biopsy, or a mammographically detected mass or calcifications, with calcifications being the most common presentation.

A central problem in the management of DCIS is the lack of understanding of its natural history and the inability to determine which DCIS will progress to invasive carcinoma during a woman's lifetime. The concordance between risk factors for DCIS and invasive carcinoma suggests that they are part of the same disease process. Attempts to better characterize the natural history of DCIS on the basis of pathologic features have not been particularly successful. The traditional morphologic classification into comedo, papillary, micropapillary, solid, and cribriform types is confounded by the observation that as many as 30% to 60% of DCIS lesions display more than one histologic pattern. To overcome this difficulty, a number of classifications based on nuclear grade and the presence or absence of necrosis have been developed.

No single classification scheme has been widely adopted, and most importantly, none of the classification systems have been prospectively demonstrated to predict the risk of development of invasive carcinoma.

Molecular profiling studies in DCIS have been limited by the need for histologic examination of the entire lesion to reliably exclude the presence of invasive carcinoma. The available data indicate that DCIS lesions share many of the genetic alterations of invasive carcinoma, but predictors of progression to invasion remain to be identified.

3.6. TNM-CLASSIFICATION

Regional Lymph Nodes

The regional lymph nodes are:

1. *Axillary* (ipsilateral): interpectoral (Rotter) nodes and lymph nodes along the axillary vein and its tributaries, which may be divided into the following levels:
    (i) Level I (low-axilla): lymph nodes lateral to the lateral border of pectoralis minor muscle
    (ii) Level II (mid-axilla): lymph nodes between the medial and lateral borders of the pectoralis minor muscle and the interpectoral (Rotter) lymph nodes
    (iii) Level III (apical axilla): apical lymph nodes and those medial to the medial margin of the pectoralis minor muscle, excluding those designated as subclavicular or infraclavicular

***Note**: Intramammary lymph nodes are coded as axillary lymph nodes Level I.*

2. *Infraclavicular (subclavicular)* (ipsilateral)
3. *Internal mammary* (ipsilateral): lymph nodes in the intercostal spaces along the edge of the sternum in the endothoracic fascia
4. *Supraclavicular* (ipsilateral)

***Note**: Any other lymph node metastasis is coded as a distant metastasis (M1), including cervical or contralateral internal mammary lymph nodes.*

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
Tis(DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget)	Paget disease of the nipple not associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumour 2 cm or less in greatest dimension

T1mi Microinvasion 0.1 cm or less in greatest dimension*

Note: **Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion,the size of only the largest focus is used to classify the microinvasion. (Do not use the sum of all individual foci.) The presence of multiple foci of microinvasion should be noted, as it is with multiple larger invasive carcinomas.*

T1a More than 0.1 cm but not more than 0.5 cm in greatest dimension

T1b More than 0.5 cm but not more than 1 cm in greatest dimension

T1c More than 1 cm but not more than 2 cm in greatest dimension

T2 Tumour more than 2 cm but not more than 5 cm in greatest dimension

T3 Tumour more than 5 cm in greatest dimension

T4 Tumour of any size with direct extension to chest wall and/or to skin (ulceration or skin nodules)

Note: *Invasion of the dermis alone does not qualify as T4. Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle T4a Extension to chest wall (does not include pectoralis muscle invasion only)*

T4b Ulceration, ipsilateral satellite skin nodules, or skin oedema

T4c Both 4a and 4b, above

T4d Inflammatory carcinoma

Note: *Inflammatory carcinoma of the breast is characterized by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. If the skin biopsy is negative and there is no localized measurable primary cancer, the T category is pTX when pathologically staging a clinical inflammatory carcinoma (T4d). Dimpling of the skin, nipple retraction, or other skin changes, except those in T4b and T4d, may occur in T1, T2, or T3 without affecting the classification.*

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed (e.g., previously removed)

N0 No regional lymph node metastasis

N1 Metastasis in movable ipsilateral Level I, II axillary lymph node(s)

N2 Metastasis in ipsilateral Level I, II axillary lymph node(s) that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary lymph node(s) in the *absence* of clinically evident axillary lymph node metastasis

N2a Metastasis in axillary lymph node(s) fixed to one another (matted) or to other structures

N2b Metastasis only in clinically detected* internal mammary lymph node(s) and in the *absence* of clinically detected axillary lymph node metastasis

N3 Metastasis in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident Level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

N3a Metastasis in infraclavicular lymph node(s)
N3b Metastasis in internal mammary and axillary lymph nodes
N3c Metastasis in supraclavicular lymph node(s)

Note: **Clinically detected is defined as detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on fine-needle aspiration biopsy with cytological examination. Confirmation of clinically detected metastatic disease by fine-needle aspiration without excision biopsy is designated with an (f) suffix, e.g., cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, e.g., cN1. Pathological classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathological T assignment.*

M – Distant Metastasis

M0 No distant metastasis
M1 Distant metastasis

pTNM Pathological Classification

pT – Primary Tumour

The pathological classification requires the examination of the primary carcinoma with no gross tumour at the margins of resection. A case can be classified pT if there is only microscopic tumour in a margin. The pT categories correspond to the T categories.

Note: *When classifying pT the tumour size is a measurement of the invasive component. If there is a large in situ component (e.g., 4 cm) and a small invasive component (e.g., 0.5 cm), the tumour is coded pT1a.*

pN – Regional Lymph Nodes

The pathological classification requires the resection and examination of at least the low axillary lymph nodes (Level I). Such a resection will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

pNX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathological study)
pN0 No regional lymph node metastasis*

Note: **Isolated tumour cell clusters (ITC) are single tumour cells or small clusters of cells not more than 0.2 mm in greatest extent that can be detected by routine H&E stains or immunohistochemistry. An additional criterion has been proposed to include a cluster of fewer than 200 cells in a single histological cross-section. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification and should be included in the total number of nodes evaluated.*

pN1 Micrometastasis; or metastasis in 1–3 axillary ipsilateral lymph nodes; and/or in internal mammary nodes with metastasis detected by sentinel lymph node biopsy but not clinically detected
pN1mi Micrometastasis (larger than 0.2 mm and/or more than 200 cells, but none larger than 2.0 mm)

pN1a Metastasis in 1–3 axillary lymph node(s), including at least 1 larger than 2 mm in greatest dimension

pN1b Internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected

pN1c Metastasis in 1–3 axillary lymph nodes and internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected

pN2 Metastasis in 4–9 ipsilateral axillary lymph nodes, or in clinically detected ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis

pN2a Metastasis in 4–9 axillary lymph nodes, including at least one that is larger than 2 mm

pN2b Metastasis in clinically detected1 internal mammary lymph node(s), in the *absence* of axillary lymph node metastasis

pN3 Metastasis as described below:

pN3a Metastasis in 10 or more axillary lymph nodes (at least one larger than 2 mm) *or* metastasis in infraclavicular lymph nodes

pN3b Metastasis in clinically detected1 internal ipsilateral mammary lymph node(s) in the *presence* of positive axillary lymph node(s); or metastasis in more than 3 axillary lymph nodes *and* in internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected

pN3c Metastasis in ipsilateral supraclavicular lymph node(s)

Grouping for stages			
Stage	**T**	**N**	**M**
0	Tis	N0	M0
IA	T1*	N0	M0
IB	T0	pN1mi	M0
	T1*	pN1mi	M0
IIA	T0	N1	M0
	T1*	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

3.7. TREATMENT

Mastectomy, excision and radiotherapy (RT), and excision alone have all been proposed as management strategies for DCIS. The appropriate therapy for the woman with DCIS depends on the extent of the DCIS lesion, the risk of local recurrence with each form of treatment, and the patient's attitude toward the risks and benefits of a particular therapy. Total or simple mastectomy is a treatment for which all women with DCIS are eligible, and it is curative in approximately 98% of patients regardless of age, DCIS presentation, size, or grade. The primary medical indication for mastectomy in DCIS is a lesion too large to be excised to negative margins with a cosmetically acceptable outcome. The extent of DCIS is most accurately estimated preoperatively with the use of magnification mammography. Conventional two-view mammography underestimates the extent of the lesion, particularly for welldifferentiated DCIS.

Initial studies indicate that MRI both overestimates and underestimates the size of DCIS lesions and does not improve surgical planning when compared with diagnostic mammography. For women with localized DCIS, management by excision alone and excision plus RT have both been employed. Four prospective, randomized trials have directly compared these two approaches in more than 4,500 patients. In all four trials, the maj ority of participants had mammographically detected DCIS, and in all but the Swedish trial, negative margins, defined as tumor-filled ducts not touching an inked surface, were required. A dose of 50 Gy of radiation was delivered to the whole breast in 25 fractions, and a boost dose to the tumor bed was not required. A tumor bed boost was employed in 9 % and 5 % of patients in the NSABP B-1 756 and European Organisation for Research and Treatment of Cancer (EORTC) 108 studies, respectively. The UK/ANZ (United Kingdom/Australia New Zealand) study has a two-by-two randomization that randomized patients to RT versus none and tamoxifen versus none, and institutions and patients could select to participate in one or both randomizations, creating imbalances between the four arms. The other studies did not allow tamoxifen. No differences in overall survival were seen between treatment arms. In all four studies, the use of RT resulted in a highly significant reduction in the risk of an ipsilateral breast tumor recurrence, with proportional risk reductions ranging from 47% in the EORTC study to 68% in the UK/ANZ study.61 Consistent with observations from many retrospective studies, approximately 50% of the recurrences in both the irradiated and the nonirradiated groups were invasive carcinoma, and a benefit for RT was seen in the reduction of both invasive and noninvasive recurrences.

Subset analyses in these trials failed to identify any patient subgroups not benefiting from RT, but emphasize that the magnitude of the benefit of RT varies with the risk of local recurrence. Patient age has been consistently identified as an important predictor of local recurrence after excision and RT.

In the NSABP B-17 trial local recurrence rates ranged from 15% in women age 49 years or less to 9% in those 60 years or older. The EORTC trial reported a relative risk of recurrence of 1.8 9 (95%CI, 1.12-3.19; P=0.026) for women aged 40 and younger in multivariate analysis. The increased incidence of local recurrence in younger women was confirmed in the NSABP B-24 trial.

Clinical presentations of DCIS were associated with a higher rate of local recurrence than mammographic ones in both the EORTC triaJ57 and the NSABP B-24 study; and both the NSABP B-17 trial and the EORTC 108 trials found high- and intermediate-grade DCIS to be more commonly associated with local recurrence than low-grade DCIS. In spite of the clear benefit of RT seen in these four trials, considerable interest in identifying patients who could be spared the cost and inconvenience of RT has persisted. In a retrospective review, Silverstein et al. 63 reported the outcome of patients with DCIS treated with and without RT and suggested that if a negative margin width of 1 em or greater was obtained, RT was not beneficial in reducing local recurrence, regardless of the characteristics of the DCIS lesion. Wong et al. 64 attempted to duplicate these findings in a prospective study of 158 patients with predominantly grade 1 and 2 DCIS who underwent excision to a negative margin greater than 1 em. The 5-year local recurrence rate was 12%, and 31% of the recurrences were invasive, resulting in premature closure of the study prior to its planned accrual of 200 patients . The Eastern Cooperative Oncology Group (ECOG) conducted a prospective, single-arm study of the outcome of excision alone in selected patients with DCIS, which involved routine detailed pathologic assessment with sequential sectioning and embedding of the complete specimen. Eligible patients included those with DCIS larger than 3 mm in size excised to a negative margin width of 3 mm or more. For patients with low- or intermediate-grade DCIS, the upper limit of lesion size was 2.5 em or less, and for those with high-grade lesions the upper size limit was 1 em or less. There were 579 patients with low- or intermediate-grade DCIS, with a median tumor size of 6 mm; 67% were excised to a margin of 5 mm or greater and 46% to a margin of 1 em or greater. At a median follow-up of 6.7 years, the 5-year rate of an ipsilateral breast event (local recurrence) was 15.3% (95% CI, 8.2%-22.5 %) for the 105 eligible patients with high-grade DCIS, and with a median follow-up of 6.2 years, the 5-year rate of an ipsilateral breast event (local recurrence) was 6.1% (95%CI, 4.1%-8.2%) for the 565 eligible patients with low- and intermediate-grade DCIS. The 101 patients with high-grade DCIS had a median tumor size of 7 mm. Seventy-five percent were excised to a margin of 5 mm or greater, and 48% had a margin of 1 em or more. In considering the results of excision alone in the low- and intermediate-grade group, it is worth noting that older studies that examined the 5-year results of the treatment of DCIS with excision and RT observed a significantly higher rate of local recurrence for high-grade DCIS compared with low- and intermediate-grade DCIS, but after 10 years of follow-up no differences in the rate of local recurrence on the basis of grade were seen.

Additional follow-up of the ECOG study will be important in determining the risks of treatment with excision alone for low- and intermediate-grade DCIS. Based on the information discussed previously, guidelines for breast-conserving surgery in DCIS developed by a joint committee of the American College of Surgeons, American College of Radiology, and College of American Pathologists recommend mastectomy for multicentric DCIS when there are diffuse malignant calcifications in the breast and when negative margins cannot be obtained. Breast-conserving surgery with radiation is recommended for those with localized DCIS excised to clear margins. Although the value of a " boost" has not been formally tested in patients with DCIS, it is generally recommended, particularly for young patients, based on trial results testing the value of a boost in patients with invasive breast cancer.

The committee acknowledged that low local recurrence rates after wide excision of low-grade DCIS have been reported, but thought that the maximum size DCIS lesion for which RT could be safely omitted was unknown. They concluded that these cases must be evaluated individually, with the patients' attitude toward risks and benefits playing a may or role in the decision to omit

3.8. RESEARCH

A considerable part of the current knowledge on breast carcinomas is based on in vivo and in vitro studies performed with breast cancer cell (BCC) lines. These provide an unlimited source of homogenous self-replicating material, free of contaminating stromal cells, and often easily cultured in simple standard media. The first line described, BT-20, was established in 1958. Since then, and despite sustained work in this area, the number of permanent lines obtained has been strikingly low (about 100). Indeed, attempts to culture BCC from primary tumors have been largely unsuccessful. This poor efficiency was often due to technical difficulties associated with the extraction of viable tumor cells from their surrounding stroma. Most of the available BCC lines issued from metastatic tumors, mainly from pleural effusions. Effusions provided generally large numbers of dissociated, viable tumor cells with little or no contamination by fibroblasts and other tumor stroma cells. Many of the currently used BCC lines were established in the late 1970s. A very few of them, namely MCF-7, T-47D, and MDA-MB-231, account for more than two-thirds of all abstracts reporting studies on mentioned BCC lines, as concluded from a Medline-based survey.

Treatments are constantly evaluated in randomized, controlled trials, to evaluate and compare individual drugs, combinations of drugs, and surgical and radiation techniques. The latest research is reported annually at scientific meetings such as that of the American Society of Clinical Oncology, San Antonio Breast Cancer Symposium, and the St. Gallen Oncology Conference in St. Gallen, Switzerland. These studies are reviewed by professional societies and other organizations, and formulated into guidelines for specific treatment groups and risk category.

3.9. QUESTIONS FOR SELF-CONTROL

1. What is the incidence rate of breast cancer in Ukraine?
2. What age is more frequent for development of breast cancer?
3. What is the stage T3N2M0 of breast cancer (explain)?
4. Name the clinical forms of breast cancer.
5. Enumerate the clinical symptoms of the nodular form of breast cancer.
6. With which diseases are nodular and diffused forms of breast cancer differentially diagnosed?
7. Make a treatment plan of stage T2N0M0 breast cancer.

3.10. TESTS FOR SELF-CONTROL

1. Early findings of carcinoma of breast include:
    a. Skin ulceration
    b. Skin retraction
    c. Single non-tender, firm to hard mass ill-defined margins
    d. All of the above
2. The most reliable diagnostic test for breast cancer is:
    a. Ultrasound of breast
    b. Mammography
    c. Fine-needle aspiration cytology
    d. Open excisional biopsy
3. Imaging of pulmonary metastases in breast cancers is done by:
    a. Mammography
    b. Spirography
    c. Chest radiography
    d. Sputum examination
4. Paget`s carcinoma is usually an infiltrating carcinoma of:
    a. Skin of axilla
    b. Lymph-nodes
    c. Breast areola
    d. Lungs
5. The early clinical sign of carcinoma of the male breast is usually:
    a. Ulceration of the nipple
    b. Umbilication symptom
    c. Bilateral masses
    d. A painless lump beneath the areola in patients over 50 years of age

Correct answers: 1c, 2d, 3c, 4c, 5d

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THEME 4

ESOPHAGEAL AND STOMACH CANCER

4.1. EPIDEMIOLOGY

The epidemiology of esophageal cancer is defined by its substantial variability as a function of histologic type, geographic area, gender, race, and ethnic background. Because of the recent increase in incidence rates of adenocarcinoma, especially in the Western hemisphere, epidemiologic studies are now distinguishing between histologic types when reporting results, whereas in the past, incidence rates of esophageal cancer reflected only squamous cell carcinoma.

This remains true in high-incidence areas where published rates are not obtained from population-based tumor registries. These high-incidence areas include Turkey, northern Iran, southern republics of the former Soviet Union, and northern China, where incidence rates exceed 100 per 100,000 person-years. Incidence rates of squamous cell carcinoma may vary 200-fold between different populations in the same geographic area because of unique cultural practices. The highest incidence rates for males (more than 15 per 100,000 person-years) reported from populationbased tumor registries were in Calvados, France; Hong Kong; and Miyagi, Japan; and the highest rates for females (more than 5 per 100,000 person-years) were in Mumbai, India; Shanghai, China; and Scotland.

Esophageal cancer is relatively uncommon in the United States, and the lifetime risk of being diagnosed with the disease is less than 1%. It was estimated that 16470 new cases would be identified in 2009, with over 14,500 patients expected to die of the disease. Age-adjusted incidence rates are highest among African American men, and the predominant histologic type is squamous cell carcinoma. The incidence rates for African American men peaked in the early 1980s, and since then they have shown a marked decline to the current rate of approximately 9 per 100000 person-years. Incidence rates among white men continue to increase and now exceed 8 per 100000 person-years, reflecting the marked increase in the incidence of adenocarcinoma of the esophagus of more than 400% in the past two decades.

Although the incidence of adenocarcinoma in white females (2 per 100000) is lower than that in white men, rates of adenocarcinoma have increased in women by more than 300% during the past 20 years. Similar trends have been noted in Western European countries. This trend of increased incidence of adenocarcinoma of the esophagus has paralleled the upward trend in rates of both gastroesophageal reflux disease and obesity.

A steady decline in esophageal cancer mortality has been noted since the mid-1980s in the nonwhite U.S. population, whereas a marked increase in mortality was noted among white men and women during the same period.

The mortality rates among African Americans exceed those for all other populations, and men fare more poorly than women.

Although survival rates for all esophageal cancer patients are uniformly dismal, regardless of race or gender, 5-year relative survival rates have significantly improved since the 1970s (5% if diagnosed in 1975 to 1977 vs. 17% if diagnosed in 1996 to 2004) based on Surveillance, Epidemiology, and End Results population-based tumor registry reporting.
There is no survival difference related to cell type (squamous cell carcinoma vs. adenocarcinoma).

4.2. ETIOLOGY, RISK FACTORS

Squamous cell carcinoma and adenocarcinoma of the esophagus share some risk factors, whereas other risk factors are specific to one histologic type or the other.

Tobacco and Alcohol Use

Tobacco and alcohol use are considered the maj or contributing factors in the development of esophageal cancer worldwide. It is estimated that up to 90% of the risk of squamous cell carcinoma of the esophagus in Western Europe and North America can be attributed to tobacco and alcohol use. Population-based studies demonstrate that tobacco and alcohol use are independent risk factors, and their effects are multiplicative, as evidenced by the association of the highest risk of developing esophageal cancer with heavy use of both agents.

Approximately 65% and 57% of squamous cell carcinomas of the esophagus have been attributed to smoking tobacco for longer than 6 months in white and African American men, respectively, in the United States. There appears to be a doseresponse effect related to the duration and intensity of smoking, and, importantly, there is an impressive (up to 50%) reduction in risk of developing squamous cell carcinoma of the esophagus for those who quit smoking and an inverse relationship between risk and the length of time since cessation of tobacco use.

Cigarette smoking in adenocarcinoma of the esophagus leads to a twofold increase in risk for heavy smokers (more than one pack per day). Quitting smoking does not appear to decrease the risk of adenocarcinoma, which remains elevated for decades after smoking cessation. This suggests that tobacco carcinogens may affect carcinogenesis early on in esophageal adenocarcinoma, and, therefore, the decline in prevalence of smoking in the United States has not had an impact on the risk for the disease.

Alcohol is a maj or contributing factor in the increased risk of esophageal squamous cell carcinoma in Western countries, likely accounting for 80% of squamous cell carcinoma of the esophagus in men in the United States.6 A dose-response relationship exists between the amount of alcohol ingested and the risk of developing squamous cell carcinoma. In most studies the most commonly consumed beverage in a specific geographic region is the one most frequently associated with increased risk.

Although specific carcinogens may be present in a variety of alcoholic beverages, in all likelihood it is alcohol itself, either as a mechanical irritant, promoter of dietary deficiency, or contributor to susceptibility to other carcinogens, that leads to carcinogenesis. Large population-based case-control studies in both the United States and Australia revealed no relationship between alcohol intake and risk of esophageal adenocarcinoma.

Diet and Nutrition

For both squamous cell carcinoma and adenocarcinoma of the esophagus, case-control studies provide evidence of a protective effect of fruits and vegetables, especially those eaten raw. These food groups contain a number of micronutrients and dietary components such as vitamins A, C, and E, selenium, carotenoids, and fiber that may prevent carcinogenesis.

Deficiencies of the aforementioned nutrients and dietary components, in particular selenium, have been associated with increased risk of esophageal squamous cell carcinoma in some parts of the world. Consumption of hot beverages has been suggested as a risk factor for esophageal cancer in South America.

Socioeconomic Status

Low socioeconomic status as defined by income, education, or occupation is associated with increased risk for esophageal squamous cell carcinoma and, to a lesser degree, for adenocarcinoma. In the United States it is estimated that 39% and 69% of squamous cell carcinomas of the esophagus in white men and African American men, respectively, are related to low annual income. A number of occupational and industrial hazards, including exposure to perchloroethylene (dry cleaners, metal polishers) , combustion products, and fossil fuels (chimney sweeps, printers, gas station attendants, asphalt and metal workers) , silica and metal dust, and asbestos, as well as viral exposure via meat packing and slaughtering, have been suggested as possible risk factors for squamous cell carcinoma but not adenocarcinoma of the esophagus .

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease has been implicated as one of the strongest risk factors for the development of adenocarcinoma of the esophagus. Chronic reflux is associated with Barrett's esophagus, the premalignant precursor of esophageal adenocarcinoma. Population-based case-control studies that examined the relationship between symptomatic reflux and risk of adenocarcinoma of the esophagus have demonstrated that increased frequency, severity, and chronicity of reflux symptoms are associated with a 2- to 16-fold increased risk of adenocarcinoma of the esophagus, regardless of the presence of Barrett's esophagus.

Trends in incidence rates of gastroesophageal reflux disease during the past three decades parallel the time trends of increasing incidence of adenocarcinoma in the United States.

Helicobacter Pylori Infection

Infection with Helicobacter pylori, and particularly with cagA+ strains, is inversely associated with the risk of adenocarcinoma of the esophagus. The mechanism of action is unclear, although H. pylori infection can result in chronic atrophic gastritis, leading to decreased acid production and potentially reducing the development of Barrett's esophagus.

Although infection by H. pylori cagA + strains by itself may not increase the risk of squamous cell carcinoma, the concurrent presence of gastric atrophy and H.pylori infection has been reported to significantly increase the risk of squamous cell carcinoma. Atrophic gastritis may promote bacterial overgrowth, leading to intragastric nitrosation, with the production of nitrosamines increasing the risk of esophageal squamous cell carcinoma.

Barrett's Esophagus

Barrett's esophagus is defined by the presence of intestinal metaplasia (mucin-producing goblet cells) in columnar celllined epithelium that replaces the normal squamous epithelium of the distal esophagus. The appearance at endoscopy of salmon-colored columnar epithelium extending about the gastroesophageal j unction contrasts with the pale, pinkcolored normal squamous pithelium of the esophagus.

Although other types of mucosa (gastric fundic or junctional type) have been identified in Barrett's esophagus, specialized intestinal metaplasia confirmed b y histologic examination of biopsy specimens is required for the diagnosis of Barrett's esophagus. A diagnosis of Barrett's esophagus confers a 40- to 125-fold higher risk of progressing to esophageal carcinoma compared with the risk in the general population and is the single most important risk factor for developing adenocarcinoma.

The absolute risk to develop adenocarcinoma in a year is approximately 1 in 200 (absolute risk, 0.5% per patient-year). Patients with short- and long-segment Barrett's esophagus are at risk of developing dysplasia and subsequently adenocarcinoma.

Achalasia

Achalasia is an idiopathic esophageal motility disorder characterized by increased basal pressure in the lower esophageal sphincter, incomplete relaxation of this sphincter after deglutition, and aperistalsis of the body of the esophagus. A 16- to 30-fold increase in esophageal squamous cancer risk has been noted in achalasia patients .

In a retrospective analysis, Aggestrup et al. observed the development of esophageal carcinomas in 10 of 147 patients undergoing esophagomyotomy for achalasia. These neoplasms are believed to result from prolonged irritation from retained food in the midesophagus and arise an average of 17 years after onset of achalasia. The chronic dysphagia and pain attributable to megaesophagus contributes to their late diagnosis in achalasia patients.

Human Papillomavirus Infection

Human papillomavirus (HPV) infection may contribute to the pathogenesis of esophageal squamous cell cancer in highincidence areas in Asia and South Africa. This oncogenic virus encodes two proteins (E6 and E7) that sequester the Rb and p53 tumor suppressor gene products. Using polymerase chain reaction techniques, de Villiers et al. detected HPV DNA sequences in 17% of esophageal squamous cell cancers in patients from China. In an additional study using similar techniques, Lavergne and de Villiers identified a broad spectrum of HPV in approximately one-third of esophageal cancer specimens obtained from patients living in high-incidence areas in China and South Africa. Shibagaki et al. detected HPV sequences in 15 of 72 (21%) esophageal cancer specimens obtained from Japanese patients. In contrast, neither evidence of HPV infection nor HPV DNA sequences have been o bs erved in cancers arising in low-incidence areas

4.3. CLINICAL PRESENTATION

The most noticeable symptoms are dysphagia and weight loss. Dysphagia signifies locally advanced disease or distant metastases, or both. Patients describe progressive dysphagia, with difficulty initially in swallowing solids, then liquids. Control of this single symptom impacts most on the patient's quality of life. Patients with squamous cell carcinoma of the esophagus more often have a history of tobacco or alcohol abuse, or both. Weight loss is seen in approximately 90% of patients with squamous cell carcinoma. Patients with adenocarcinoma of the esophagus tend to be white males from middle to upper socioeconomic classes who are overweight, have a symptomatic gastroesophageal reflux, and have been treated with antireflux therapy.

Approximately 20% of patients experience odynophagia (painful swallowing). Additional presenting symptoms include dull retrosternal pain, bone pain secondary to bone metastases, and cough or hoarseness secondary to paratracheal nodal or recurrent laryngeal nerve involvement. These types of symptoms suggest unresectable locally advanced disease or metastases. Unusual presentations are pneumonia secondary to tracheoesophageal fistula or exsanguinating hemorrhage due to aortic invaston.

4.4. DIAGNOSTICS

Patients with symptoms of dysphagia should undergo upper endoscopy and biopsy to establish a tissue diagnosis. Biopsies or cytologic brushings have a diagnostic accuracy approaching 100%. Targeted biopsy can be enhanced by the use of chromoendoscopy techniques using vital dyes, including indigo carmine, Lugol's iodine solution, methylene blue, and toluidine blue.

Autofluorescence imaging and narrow band imaging are emerging endoscopic techniques that allow for detailed inspection of mucosa. A focused history taking should elicit information on predisposing factors for esophageal cancer, including tobacco use, alcohol use, symptomatic reflux, diagnosis of Barrett's esophagus, and history of head and neck or thoracic malignancy.

Prior surgery on the stomach or colon may influence the choice of reconstructive conduit to restore alimentary continuity at the time of esophagectomy. Findings on history and physical examination that would prompt further diagnostic testing include hoarseness, cervical or supraclavicular lymphadenopathy, pleural effusion, or new onset of bone pain.

Chest radiography and liquid oral contrast examination of the esophagus and stomach have been replaced by computed tomography (CT) and flexible endoscopy. Esophagogastroscopy allows precise evaluation of the extent of esophageal and gastric involvement and can precisely measure the distance of the tumor from the incisors to appropriately categorize the tumor's location. Upper endoscopy also allows identification of "skip" lesions or second primaries as well as indicates the presence and extent of Barrett's esophagus. Bronchoscopy should be reserved for those patients with tumors of the middle and upper esophagus to rule out invasion of the membranous trachea and possible tracheoesophageal fistula.

Pretreatment staging procedures establish the depth of esophageal wall penetration, regional lymph nodes, and the presence distant metastases so that patients can be guided to appropriate treatment. CT scan of the chest and abdomen is mandatory. A recent single institution review of 201 CT scans in 99 patients undergoing staging for esophageal cancer indicated that imaging of the pelvis did not contribute added staging information, and it may not need to be routinely performed. 115 CT scans are highly accurate (approaching 100%) in detecting liver or lung metastases and suggesting peritoneal carcinomatosis (e.g., ascites, omental infiltration, peritoneal tumor studding).

Accuracy for detecting aortic involvement or tracheobronchial invasion exceeds 90%. CT is inaccurate in determining T stage and N stage. The accuracy of endoscopic ultrasonography (EUS) in determining both T and N stage is a function of its ability to clearly delineate the multiple layers of the esophageal wall and its use of multiple criteria, including shape, border pattern, echogenicity, and size, to determine lymph node involvement. EUS is superior to CT in both T and N staging of esophageal cancer.

The overall accuracy for T staging is approximately 85% and for N staging it is approximately 75%. The accuracy of determining lymph node involvement has been increased to 85% to 100% with the use of linear-array EUS with a channel that allows passage of a needle to perform tissue aspiration for cytology. EUS is highly operator dependent and is limited in its ability to define relatively superficial lesions as either T1 or T2. This distinction is critical to allow the use of minimal resection techniques for T1 lesions and to avoid preoperative chemoradiation for T1 and T2 tumors. Mini probe high-frequency (20 MHz) sonographic catheters that can be passed through the working channel of the standard endoscope are now being used and provide improved accuracy.

A new generation of endoscopes that are thin caliber may traverse almost all obstructing lesions, allowing EUS assessment. The accuracy of EUS in assessing response to induction chemoradiation is severely limited, and its use frequently leads to overstaging because the fibrotic changes induced by treatment mimic residual tumor, although recent data may indicate some utility for posttherapy EUS.

Fluorine-18 (18F) fluorodeoxyglucose (FDG) positron emission tomography (PET) is being widely applied in the management of esophageal cancer. The accuracy of FDG-PET in assessing regional lymph nodes falls somewhere between the low and high accuracy of CT and EUS, respectively. In the detection of distant metastases, FDG-PET is superior to CT, with a sensitivity, specificity, and accuracy all in the range of 80% to 90%. PET in combination with CT (PET-CT fusion or hybrid FDG-PET/CT) further improves specificity and accuracy of noninvasive staging. This leads to detection of unsuspected metastatic disease (up-staging) in 15% of patients, which leads to alteration of the intended treatment plan in at least 20% of patients. FDG-PET may also have value in evaluating response to chemotherapy and radiotherapy.

Weber et al. demonstrated that decreased FDG uptake significantly correlated with pathologically confirmed response in p atients treated with induction chemotherapy before esophagectomy for esophageal adenocarcinoma.

A prospective validation study confirmed that a decrease in the standard uptake value of 35% or more during preoperative chemotherapy may predict histologic response and is associated with improved survival and decreased recurrence. Brucher et al., from the same institution, Technische Universitat Munchen, showed a similar result of decreased FDG uptake in responders compared with nonresponders in patients with squamous cell carcinoma of the esophagus treated with preoperative chemoradiation. A recent trial from the Munich group led by Lordick et al. examined PET scan response during induction chemotherapy in 110 patients with adenocarcinoma of the gastroesophageal junction. PET scan nonresponders (54 patients) assessed after 2 weeks of induction chemotherapy were referred for immediate surgery rather than continuing with the full 3-month course of preoperative chemotherapy.

Survival in these patients (median 26 months) was comparable to nonresponding patients in a preceding trial (median 18 months) who continued the full 3 months of chemotherapy prior to surgery, indicating that discontinuation of an ineffective therapy and referral for earlier surgery did not compromise outcome. Survival, however, was inferior in the PET nonresponding patients compared with the PET responders. Although PET response may identify patients in whom ineffective preoperative therapy should be discontinued, whether or not referral of such patients for alternative chemotherapy, or chemoradiation, is warranted remains to be established.

One series of patients treated with induction chemotherapy, followed with serial PET scans, identified some patients who progressed on induction chemotherapy. Several of these patients achieved durable disease control, including pathologic complete response, when changed to an alternative chemotherapy during radiation therapy, suggesting that salvage with alternative treatment may be possible.

Two recent systematic reviews of the current available literature that addressed the evaluation of tumor response by PET to neoadjuvant therapy concluded that while PET is the best imaging modality available to assess response, the current data do not support recommending the routine use of PET scans to guide therapeutic decisions. Currently, the utility of PET to detect distant disease not identified by other imaging modalities confirms a role for PET that is complementary to other staging procedures, although it should not supplant them.

Minimally invasive surgical techniques (laparoscopy, thoracoscopy, or both) are being used for staging of both locoregional and distant disease. Performing laparoscopy as the initial procedure at the time of planned esophagectomy adds little in the way of time and cost to the procedure and allows detection of unsuspected distant metastases, which spares the morbidity of laparotomy in 10% to 15% of cases. Although studies suggest improved pretreatment staging with minimally invasive surgical approaches, such approaches have not been embraced because of the morbidity, length of hospital stay, and cost associated with what is considered an additional procedure.

A study comparing the health care costs and efficacy of staging procedures, including CT scan, EUS fine-needle aspiration (FNA), PET, and thoracoscopy or laparoscopy reported that CT plus EUS FNA was the least expensive and offered the most quality-adj usted life-years on average than all the other strategies. PET plus EUS FNA was somewhat more effective but also more expensive

4.4. TNM-CLASSIFICATION

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ/high-grade dysplasia
T1	Tumour invades lamina propria, muscularis mucosae, or submucosa

T1a	Tumour invades lamina propria or muscularis mucosae
T1b	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades adventitia
T4	Tumour invades adjacent structures
T4a	Tumour invades pleura, pericardium, or diaphragm
T4b	Tumour invades other adjacent structures such as aorta, vertebral body, or trachea

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes

M – Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis

Groupiung for stages

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
IIIA	T4a	N0	M0
	T3	N1	M0
	T1	N2	M0
	T2	N2	M0
IIIB	T3	N2	M0
IIIC	T4a	N1	M0
	T4a	N2	M0
	T4b	Any N	M0
	Any T	N3	M0
IV	Any T	Any N	M1

4.5. TREATMENT

General approaches

Esophageal cancer affecting the lower esophagus. Insets show the tumor in more detail both before and after placement of a stent.

The treatment is determined by the cellular type of cancer (adenocarcinoma or squamous cell carcinoma vs other types), the stage of the disease, the general condition of the patient and other diseases present. On the whole, adequate nutrition needs to be assured, and adequate dental care is vital.

If the patient cannot swallow at all, an esophageal stent may be inserted to keep the esophagus patent; stents may also assist in occluding fistulas. A nasogastric tube may be necessary to continue feeding while treatment for the tumor is given, and some patients require a gastrostomy (feeding hole in the skin that gives direct access to the stomach). The latter two are especially important if the patient tends to aspirate food or saliva into the airways, predisposing for aspiration pneumonia.

Esophagectomy is the removal of a segment of the esophagus; as this shortens the length of the remaining esophagus, some other segment of the digestive tract (typically the stomach or part of the colon or jejunum) is pulled up to the chest cavity and interposed.[24] If the tumor is unresectable or the patient is not fit for surgery, palliative esophageal stenting can allow the patient to tolerate soft diet.

Types of esophagectomy:

The thoracoabdominal approach opens the abdominal and thoracic cavities together.

The two-stage Ivor Lewis (also called Lewis–Tanner) approach involves an initial laparotomy and construction of a gastric tube, followed by a right thoracotomy to excise the tumor and create an esophagogastric anastomosis.

The three-stage McKeown approach adds a third incision in the neck to complete the cervical anastomosis.

Data are accumulating to indicate endoscopic therapy is a safe, less invasive, and effective therapy for very early esophageal cancer. The candidates for endoscopic therapy are Stage 1 patients with tumors invading into the lamina propria (T1 mucosal) or submucosa (T1 submucosal) that do not have regional or distant metastasis. Patients with carcinoma in situ or high-grade dysplasia can also be treated with endoscopic therapy. Submucosal cancers with increased risk of nodal metastases may not be as amenable to curative therapy.

Forms of endoscopic therapy have been used for Stage 0 and I disease: endoscopic mucosal resection (EMR) and mucosal ablation using radiofrequency ablation, photodynamic therapy, Nd-YAG laser, or argon plasma coagulation.

EMR has been advocated for early cancers (that is, those that are superficial and confined to the mucosa only) and has been shown to be a less invasive, safe, and highly effective nonsurgical therapy for early squamous cell esophageal cancer.

It has also been shown to have be safe and effective for early adenocarcinoma arising in Barrett's esophagus. The prognosis after treatment with EMR is comparable to surgical resection. This technique can be attempted in patients, without evidence of nodal or distant metastases, with differentiated tumors that are slightly raised and less than 2 cm in diameter, or in differentiated tumors that are ulcerated and less than 1 cm in diameter. The most commonly employed modalities of EMR include strip biopsy, double-snare polypectomy, resection with combined use of highly concentrated saline and epinephrine, and resection using a cap.

The strip biopsy method for endoscopic mucosal resection of esophageal cancer is performed with a double-channel endoscope equipped with grasping forceps and snare. After marking the lesion border with an electric coagulator, saline is injected into the submucosa below the lesion to separate the lesion from the muscle layer and to force its protrusion. The grasping forceps are passed through the snare loop. The mucosa surrounding the lesion is grasped, lifted, and strangulated and resected by electrocautery. The endoscopic double-snare polypectomy method is indicated for protruding lesions. Using a double-channel scope, the lesion is grasped and lifted by the first snare and strangulated with the second snare for complete resection.

Endoscopic resection with injection of concentrated saline and epinephrine is carried out using a double-channel scope. The lesion borders are marked with a coagulator. Highly concentrated saline and epinephrine are injected (15–20 ml) into the submucosal layer to swell the area containing the lesion and elucidate the markings. The mucosa outside the demarcated border is excised using a high-frequency scalpel to the depth of the submucosal layer. The resected mucosa is lifted and grasped with forceps, trapping and strangulating the lesion with a snare, and then resected by electrocautery.

Another method of EMR employs the use of a clear cap and prelooped snare inside the cap. After insertion, the cap is placed on the lesion and the mucosa containing the lesion is drawn up inside the cap by aspiration. The mucosa is caught by the snare and strangulated, and finally resected by electrocautery. This is called the "band and snare" or "suck and cut" technique. The resected specimen is retrieved and submitted for microscopic examination for determination of tumor invasion depth, resection margin, and possible vascular involvement. The resulting "ulcer" heals within three weeks.

EMR can also be used to debulk or completely treat polypoid dysplastic or malignant lesions in Barrett's esophagus, the known precursor lesion to esophageal adenocarcinoma. In a preliminary report from Germany, EMR was performed as primary treatment or adjunctive therapy following photodynamic therapy for early adenocarcinomas in Barrett's esophagus. The "suck and cut" technique (with and without prior saline injection) was used, as well as the "band and cut" technique. Although all tumors were resected without difficulty, 12.5% developed bleeding (which was managed successfully by endoscopic therapy).

Eighty-one percent of the lesions were completely resected. The other lesions were also treated with other endoscopic techniques.

The major complications of endoscopic mucosal resection include postoperative bleeding, perforation and stricture formation. During the procedure, an injection of 100,000 times diluted epinephrine into the muscular wall, along with high-frequency coagulation or clipping can be applied to the bleeding point for hemostasis. It is important to administer acid-reducing medications to prevent postoperative hemorrhage. Perforation may be prevented with sufficient saline injection to raise the mucosa containing the lesion. The "non-lifting sign" and complaints of pain when the snare strangulates the lesion are contraindications of EMR. When perforation is recognized immediately after a procedure, the perforation should be closed by clips. Surgery should be considered in cases of endoscopic closure failure. The incidence of complications ranges from 0–50% and squamous cell recurrence rates range from 0–8%.

Laser therapy is the use of high-intensity light to destroy tumor cells; it affects only the treated area. This is typically done if the cancer cannot be removed by surgery. The relief of a blockage can help to reduce dysphagia and pain. Photodynamic therapy, a type of laser therapy, involves the use of drugs that are absorbed by cancer cells; when exposed to a special light, the drugs become active and destroy the cancer cells.

Chemotherapy depends on the tumor type, but tends to be cisplatin-based (or carboplatin or oxaliplatin) every three weeks with fluorouracil (5-FU) either continuously or every three weeks. In more recent studies, addition of epirubicin was better than other comparable regimens in advanced nonresectable cancer.[25] Chemotherapy may be given after surgery (adjuvant, i.e. to reduce risk of recurrence), before surgery (neoadjuvant) or if surgery is not possible; in this case, cisplatin and 5-FU are used. Ongoing trials compare various combinations of chemotherapy; the phase II/III REAL-2 trial – for example – compares four regimens containing epirubicin and either cisplatin or oxaliplatin, and either continuously infused fluorouracil or capecitabine.

Radiotherapy is given before, during or after chemotherapy or surgery, and sometimes on its own to control symptoms. In patients with localized disease but contraindications to surgery, "radical radiotherapy" may be used with curative intent.

Radiofrequency ablation is a new treatment modality for the treatment of Barrett's esophagus and dysplasia, and has been the subject of numerous published clinical trials. The findings demonstrate radiofrequency ablation has an efficacy of 80–90% or greater with respect to complete clearance of Barrett's esophagus and dysplasia with durability up to 5 years and a favorable safety profile. Recent clinical trials have shown that endoscopic resection of esophageal mucosal irregularities and nodules which contain dysplasia or carcinoma combined with subsequent radiofrequency ablation of the remaining flat Barrett's esophagus and dysplasia can effectively and safely eradicate the disease.

Further, a recent multicenter randomized control trial found that in patients with Barrett's esophagus containing nodules or mucosal irregularities which contained high grade dysplasia or cancer, subsequent radiofrequency ablation resulted not only in eradication of Barrett's esophagus and dysplasia, but had significantly less esophageal stricture versus patients who had circumferential endoscopic mucosal resection for their disease.

4.6. PROGNOSIS

In general, the prognosis of esophageal cancer is quite poor, because most patients present with advanced disease. By the time the first symptoms such as dysphagia start manifesting themselves, the cancer has already well progressed. The overall five-year survival rate (5YSR) is approximately 15%, with most patients dying within the first year of diagnosis.

Individualized prognosis depends largely on stage. Those with cancer restricted entirely to the esophageal mucosa have about an 80% 5YSR, but submucosal involvement brings this down to less than 50%. Extension into the muscularispropria (muscular layer of the esophagus) has meant a 20% 5YSR and extension to the structures adjacent to the esophagus results in a 7% 5YSR. Patients with distant metastases (who are not candidates for curative surgery) have a less than 3% 5YSR.

4.7. QUESTIONS FOR SELF-CONTROL

1. Name countries with the highest incidence of esophageal cancer.
2. What causes esophageal cancer (risk factors)?
3. What are the main pre-cancerous diseases of the esophagus?
4. What parts of the esophagus are affected by cancer more frequently?
5. What are the symptoms of esophageal cancer?
6. How is the esophageal cancer diagnosed?
7. How is the esophageal cancer treated?

4.8. TESTS FOR SELF-CONTROL

1. Improved survival rates in patients of esophageal cancers are seen in:
    a. Radiation therapy
    b. Chemotherapy
    c. Surgical resection after radiation therapy
    d. Surgical resection at the very early stages
2. Deficiencies of ….have been implicated in the development of esophageal cancers.
    a. Folic acid

   b. Vitamin B6 or B12
   c. Calcium
   d. Fiber intake
3. The most common histological type of low esophageal cancer is:
   a. Squamous cell carcinoma
   b. Spindle cell carcinoma
   c. Adenocarcinoma
   d. Mucoepidermoidal carcinoma
4. Most common symptoms of esophageal cancer at the time of its presentation are:
   a. Excruciating cough
   b. Thoracic mass
   c. Dysphagia
   d. Loss of appetite
5. Histological finding at Barrett`s esophagus is:
   a. A malignant tumour
   b. A dysplasia of esophageal lining
   c. A metaplasia of squamous epithelium to columnar epithelium
   d. None of the above

Correct answers: 1d, 2a, 3c, 4c, 5c

STOMACH CANCER

4.9. EPIDEMIOLOGY, ETIOLOGY

The incidence and mortality rates for gastric cancer vary widely in different regions of the world. The highest incidences of stomach cancer can be found in Japan, Southeast Asia, South America, and Eastern Europe, with incidence rates as high as 30 to 85 cases per 100000 population. Almost two-thirds of the cases occur in developing countries with 42% in China alone.

In contrast, low-incidence areas such as the United States, Israel, Australia, New Zealand, and Kuwait have incidence rates of less than 10 cases per 100000. However, recent data suggest that the incidence of gastric cancer in the United States has increased by almost 60% over the past decade for ages 25 to 39 years. Mortality figures approach incidence figures in many high-incidence countries. In Japan, there has been a continuous decline in mortality, perhaps as a result of mass screening and early detection. Immigrants gradually acquire the incidence rates of the country to which they move, suggesting that environmental factors are important in etiology. Japanese persons migrating to lower risk areas had a risk of stomach cancer intermediate between that of the Western population and that of the Japanese population in Japan. The risk of stomach cancer was high in second-generation offspring who continued to consume a Japanese-style diet but was low in those adopting a Westernstyle diet.

A study of Polish and Portuguese migrants living in the United States found that the incidence of gastric cancer decreased and became intermediate between the usual incidences in the countries of origin and adoption. These studies suggest that environmental exposure in early life is essential in determining risk, but other environmental or cultural factors contribute to the predisposition to cancer. In the United States, gastric cancer is now the sixth most common cause of cancer-related death, although a century ago it was the most common cause. Incidence rates increase and survival decreases with increasing age of the population. There are substantial racial variations in incidence and death rates. The highest death rates are among African American men (11 cases per 100000 population annually), followed by Asian American men (10 cases per 100000), and American Indian and Alaskan men (9-10 cases per 100000). The lowest incidence rates are recorded among white American women (2.5 cases per 100000).

U.S. survival statistics have shown improvement in 5-year survival rates over the past two decades for all cancers from 50% in 1975 to 68 % in 2006. The reason for this improvement is not clear. Surveillance, Epidemiology, and End Results (SEER) cancer statistics showed a 15.4% 5-year relative overall survival rate in 1973 compared with 26.7% by 2006. Survival rates are best in the groups with the lowest incidence of gastric cancer.

One of the most striking epidemiologic observations has been the increasing incidence of adenocarcinomas of the proximal stomach and distal esophagus.

These tumors are thought to have different etiologic factors than distal gastric cancers. Gastric body lesions are associated with low acid production and Helicobacter pylori infection, whereas cardia lesions are not associated with either. Potentially, the improvements in treatment for H. pylori resulted in decreased frequency of noncardia lesions while at the same time decreasing the protection for distal esophagus and cardia cancers due to decreased acid production and reflux in patients with H.pylori infection and atrophic gastritis. Cardia lesions also have a higher male to female ratio and are more common in whites than in African Americans. In 2009, Wu et al., reviewing the SEER database, reported that between 1978 and 2005, total cases of gastric cancer decreased by 34% .

Regardless of site, intestinal type rates decreased by 44% , whereas diffuse type increased by 62% up to 2000 and modestly declined in recent years. Cardia cancers increased by 23 % mostly during the 1980s, and noncardia cancers declined consistently. When considered by type and site, diffuse type increased by 77% for cardia cancers. Intestinal-type rates decreased by 40% for all sites except cardia, which increased by 17%.

Rates for all types were higher among males than females. Intestinal type and noncardia site were highest among blacks and lowest among white females. Diffuse type was highest among nonwhites. Cardia site were highest among white males and lowest among all females. Noncardia site among nonwhites were double to triple those among whites. The maj ority of gastric cancers are adenocarcinomas.

The " intestinal" type frequently arises in the body/antrum. Prior infection with H. pylori, especially cagA(+). A subtype, has been associated with an increased risk of the intestinal type. Diffuse (signet cell) gastric cancer may develop in any part of the stomach, has no clear link to H. pylori infection, and is associated in a small percentage with CDHl mutation, which encodes for E-cadherin (hereditary diffuse gastric cancer). Silencing of CDH1 by methylation is also associated with the sporadic form of diffuse gastric cancer.

4.10. CLINICAL PRESENTATION

Because of the vague, nonspecific symptoms that characterize gastric cancer, many patients are diagnosed with advancedstage disease. Patients may have a combination of signs and symptoms such as weight loss (22%-61%); anorexia (5%-40%); fatigue, epigastric discomfort, or pain (62%-91%); postprand fullness, heart burn, indigestion, nausea and vomiting (6%-40%); none of these unequivocally indicates gastric cancer. In addition, patients may be asymptomatic (4%-17%).

Weight loss and abdominal pain are the most common presenting symptoms at initial encounter. Weight loss is a common symptom, and its clinical significance should not be underestimated. Dewys et al. found that in 179 patients with advanced gastric cancer, more than 80% of patients had a greater than 10% decrease in body weight before diagnosis.

Furthermore, patients with weight loss had a significantly shorter survival than did those without weight loss. In some patients, symptoms may suggest the presence of a lesion at a specific location. Up to 25% of the patients have histology/symptoms of peptic ulcer disease. A history of dysphagia or pseudoachalasia may indicate the presence of a tumor in the cardia with extension through the gastroesophageal junction. Early satiety is an infrequent symptom of gastric cancer but is indicative of a diffusely infiltrative tumor that has resulted in loss of distensibility of the gastric wall. Later satiety and vomiting may indicate pyloric involvement. Significant gastrointestinal bleeding is uncommon with gastric cancer; however, hematemesis does occur in approximately 10% to 15% of patients, and anemia in 1% to 12% of patients. Signs and symptoms at presentation are often related to spread of disease.

Ascites, jaundice, or a palpable mass indicates incurable disease. The transverse colon is a potential site of malignant fistulization and obstruction from a gastric primary tumor. Diffuse peritoneal spread of disease frequently produces other sites of intestinal obstruction. A large ovarian mass (Krukenberg's tumor) or a large peritoneal implant in the pelvis (Blumer's shelf), which can produce symptoms of rectal obstruction, may be felt on pelvic or rectal examination. Nodular metastases in the subcutaneous tissue around the umbilicus (Sister Mary Joseph's node) or in peripheral lymph nodes such as in the supraclavicular area (Virchow's node) represent areas in which a tissue diagnosis can be established with minimal morbidity.

There is no symptom complex that occurs early in the evolution of gastric cancer that can identify individuals for further diagnostic measures. However, alarm symptoms (dysphagia, weight loss, and palpable abdominal mass) are independently associated with survival; increased number and the specific symptom correlate with mortality

4.11. DIAGNOSTICS

Tumor Markers

Most gastric cancers have at least one elevated tumor marker, but some benign gastric diseases show elevated tumor markers as well. Tumor markers in gastric cancer continue to have limited diagnostic usefulness, with their role more helpful in follow-up . The most commonly used markers are CEA, CA 19-9, CA 50, and CA 72-4. There is wide variation in the reported serum levels of these markers; positive CEA and CA 19-9 levels varied from 8% to 58% and 4% to 65%, respectively. Overall, the sensitivity of each tumor marker alone as a diagnostic marker of gastric cancer is low. However, when the levels are elevated, it does usually correlate with stage.

Combining CEA with other markers, such as the CA 19-9, CA 72-4, or CA 50, can increase sensitivity compared with CEA alone In a large study evaluating CEA, a-fetoprotein, human chronic gonadotropin-3 (3-HCG), CA 19-9, CA 125, as well as tissue staining for HER2 in gastric cancer patients, only 3-HCG level greater than 4 IU/L, and a CA 125 level equal to or greater than 350 U/mL had prognostic significance. Elevated serum tumor marker levels in gastric cancer before chemotherapy may reflect not just tumor burden but also biology.

Endoscopy

Endoscopy is the best method to diagnose gastric cancer as it visualizes the gastric mucosa and allows biopsy for a histologic diagnosis. Chromoendoscopy helps identification of mucosal abnormalities through topical stains. Magnification endoscopy is used to magnify standard endoscopic fields by 1.5- to 150-fold. Narrow band imaging affords increased visualization of the microvasculature. Confocal laser endomicroscopy permits in vivo, three-dimensional microscopy including subsurface structures with diagnostic accuracy, sensitivity, and specificity of 97%, 90%, and 99.5%, respectively. Endoscopic ultrasound (EUS) is a tool for preoperative staging and selection for neoadjuvant therapy. It is used to assess the T and N stage. A study of 225 patients from MSKCC found that the concordance between EUS and pathology was lower than expected. The accuracy for individual T and N stage were 57% and 50%, respectively. However, the combined assessment of N stage and serosal invasion identified 77% of the patients at risk of death after curative resection. Other investigators compared the accuracy of EUS with that of multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) and found that the overall accuracy was 65 % to 92% , 77% to 89%, and 71% to 83% for T stage, and 55% to 66%, 32% to 77% for N stage, respectively. The corresponding sensitivity and specificity for serosal involvement were 78% to 100%, 83% to 100%, and 89% to 93% for T stage, and 68% to 100% , 80% to 97%, and 91% to 100% for N stage, respectively.

Computed Tomography

Once gastric cancer is suspected, a triphasic CT with oral and intravenous contrast of the abdomen, chest, and pelvis is imperative. In a study of 790 patients who underwent MDCT prior to surgery, the overall accuracy in determining T stage was 74% (T1 46%, T2 53% , T3 86%, and T4 86%), and for N staging it was 75% (N0 76% , N1 69% , and N2 80%). The sensitivity, specificity, and accuracy for lymph node metastasis were 86%, 76%, and 82%, respectively. MDCT with thin-sliced multiplanar reconstruction (MPR) and water filling is increasingly used. The accuracy rate for advanced gastric cancer was 96% and for early gastric cancer it was 41% . An improvement on axial CT and MPR-MDCT was the addition of staging with three-dimensional MPR-MDCT.

The detection rate for MPR with virtual gastroscopy was 98%. MPR-MDCT with combined water and air distention is superior to conventional axial imaging.

Magnetic Resonance Imaging

MRI is not used routinely in preoperative staging of gastric cancer. Several studies have demonstrated that CT and MRI are comparable in terms of accuracy and understaging. However, MRI i s a useful modality t o further characterize liver lesions identified on preoperative CT staging workup.

Positron Emission Tomography

Whole-body 2-[18F]-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) is being applied increasingly in the evaluation of gastrointestinal malignancies. In gastric cancer, approximately half of the primary tumors are FDG-negative; the diffuse (signet cell) subtype was most likely to be non-FDG avid, likely because of decreased expression of the glucose transporter-1 (Glut-1). In patients with non-FDG avid primary tumor, FDG-PET/CT is not useful. PET/CT was tested as a tool to predict response to neoadjuvant chemotherapy. Ott et al. reported 90% 2-year survival in patients with PET-defined response (<35% decrease standardized uptake value [SUV]) versus 25% for patients not responding to PET.

PET response could be detected as early as 14 days. At least 60% of the patients were PET-nonresponding patients and thus could have been spared further chemotherapy. Authors of the MUNICON trial reported on patients who were PET nonresponders by day 14 after cisplatin and fluorouracil (5-FU) neoadj uvant chemotherapy and subsequently were sent for surgery, and patients who were PET responders and continued 3 months of neoadj uvant therapy before surgery. The PETresponding patients had a survival benefit (hazard ratio [HR] 2.13; P<0.15). In PET-nonresponding patients, stopping the chemotherapy did not affect long-term survival. Recent studies, including one large meta-analysis, showed that in terms of diagnostic accuracy and lymph node staging EUS, MDCT, MRI, and PET/CT are comparable modalities. There were no significant differences between mean sens itivities and specificities. Even in patients whose tumors were FDG avid, FDG-PET/CT scans did not identify occult peritoneal disease (0 of 18) but did identify extraperitoneal M 1 disease in nine patients with bone (n = 2), liver (n = 4), and retroperitoneal lymph node (n = 3) involvement. In patients with FDG avid tumors, PET may be useful in detecting metastatic disease and follow-up for recurrence, Interestingly, the presence of glucose transporter- 1 and FDG-avid gastric cancers may be associated with decreased overall survival. The role of PET/CT in the primary staging of gastric cancer remains to be established; its role might be better defined in advanced disease.

Staging Laparoscopy and Peritoneal Cytology

Staging laparoscopy with peritoneal lavage should be an integral part of the pretreatment staging evaluation of patients believed to have localized gastric cancer. Current noninvasive modalities used in preoperative staging of gastric cancer have sensitivities significantly lower than 100%, particularly in cases of low-volume peritoneal carcinomatosis. Current CT techniques cannot consistently identify low-volume macroscopic metastases that are 5 mm or less in size. Laparoscopy directly inspects the peritoneal and visceral surfaces for detection of CT-occult, small-volume metastases. Staging laparoscopy also allows for assessment of peritoneal cytology and laparoscopic ultrasound. Laparoscopic staging is done to spare nontherapeutic operations and for potential stratification in various trials.

The rate of detection of CT-occult M1 disease by laparoscopy depends on the quality of CT scanning and interpretation. Muntean et al. reported on 98 patients with primary gastric cancer, 45 underwent staging laparoscopy with subsequent surgery and 53 went directly to surgery. An unnecessary laparotomy was avoided in 38% of the patients. The overall sensitivity and specificity were 89% and 100%, respectively.

Nonetheless, even high-quality MDCT is insufficiently sensitive for detection of low-volume extragastric disease and thus CT, EUS, and laparoscopy are complementary staging studies.

The value of peritoneal cytology as a preoperative staging tool in patients with gastric cancer who are potential candidates for curative resection by EUS and CT has been examined by several investigators. Bentrem et al. reported on 371 patients who underwent R0 resection, 6.5% of whom had positive cytology after staging laparoscopy. Median survival of patients with positive cytology was 14.8 versus 98.5 months for patients with negative cytology findings ($P<.001$). Positive cytology predicted death from gastric cancer (RR, 2.7; $P<.001$). Several groups confirmed these findings and concluded that staging laparoscopy with peritoneal cytology can change the management of gastric cancer in 6.5% to 52% of patients. Laparoscopy can be performed as a separate staging procedure prior to definitive treatment planning or immediately prior to planned laparotomy for gastrectomy. When performed as a separate procedure, laparoscopy has the disadvantage of the additional risks and expense of a second general anesthetic.

However, separate procedure laparoscopy allows the additional staging information including cytology acquired at laparoscopy to be reviewed and discussed with the patient and multidisciplinary treatment group prior to definitive treatment planning. Laparoscopic ultrasound (LUS) and "extended laparoscopy" are techniques that may increase the diagnostic yield of laparoscopy laparoscopy.

Preliminary results reveal conflicting data on the added benefit of LUS and extended laparoscopy. Further prospective studies will be required to evaluate the cost-benefit relationship of LUS and extended laparoscopy in the routine or selective workup of patients with gastric cancer.

Although laparoscopic staging is thought to detect CT-occult metastatic disease in approximately 40% of patients and spares nontherapeutic operations in approximately one-third of gastric cancer patients, one needs to remember that tumor biology, not staging, will eventually guide outcomes. Clearly, not all patients benefit from preoperative laparoscopic staging; therefore, future studies should address the issue of selective laparoscopy based on noninvasive staging (i.e., patients with T1 tumors) . Staging laparoscopy with or without cytology should be considered only if therapy will be altered consequent to information obtained by laparoscopy

4.12. TNM-CLASSIFICATION

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria, high grade dysplasia
T1	Tumour invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumour invades lamina propria or muscularis mucosae
T1b	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades subserosa
T4	Tumour perforates serosa or invades adjacent structures[1, 2, 3]
T4a	Tumour perforates serosa
T4b	Tumour invades adjacent structures[1, 2, 3]

Notes: *1. The adjacent structures of the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.*
2. Intramural extension to the duodenum or oesophagus is classified by the depth of greatest invasion in any of these sites, including stomach.
3. Tumour that extends into gastrocolic or gastrohepatic ligaments or into greater or lesser omentum, without perforation of visceral peritoneum, is T3.

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 2 regional lymph nodes
N2	Metastasis in 3 to 6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes

M – Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis

Note: *Distant metastasis includes peritoneal seeding, positive peritoneal cytology, and omental tumour not part of continuous extension.*

Grouping for stages

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
IIIA	T4a	N0	M0
	T3	N1	M0
	T1	N2	M0
	T2	N2	M0
IIIB	T3	N2	M0
IIIC	T4a	N1	M0
	T4a	N2	M0
	T4b	Any N	M0
	Any T	N3	M0
IV	Any T	Any N	M1

Japanese Staging System

The most recent japanese Classification for Gastric Carcinoma was published in 1998. The Japanese classification and staging system is more detailed than the AJCC/UICC staging system and places more emphasis on the distinction between clinical, surgical, pathologic, and "final" staging (prefixes "c", "s", "p" and "f" respectively). The Japanese classification system also includes a classification system for early gastric cancer.

Similar to the AJCC/UICC staging system, primary tumor (T) stage in the Japanese system is based on the depth of invasion and extension to adj acent structures. However, the assignment of lymph node (N) stage involves much more rigorous pathologic assessment than is required for AJCC/UICC staging. The Japanese system extensively classifies 18 lymph node regions into four N categories (N0 to N3) depending on their relationship to the primary tumor and anatomic location.

Most perigastric lymph nodes (nodal stations 1 through 6) are considered group N1. Lymph nodes situated along the proximal left gastric artery (station 7), common hepatic artery (8), celiac axis (9), splenic artery (11), and proper hepatic artery (12) are defined as group N2.

Para-aortic lymph nodes (16) are defined as group N3. However, some lymph nodes, even perigastric nodes for specific tumor locations, can be regarded as M1 disease. This is because their involvement in antral tumors is rare and portrays a bad prognosis .

The Japanese staging system also includes elements not included in the AJCC/UICC system. These are macroscopic description of the tumor (early gastric cancer subtype or Borrmann type for more advanced tumors) , extent of peritoneal metastases (classified as PO-1), extent of hepatic metastases (H0-1), and peritoneal cytology findings (CY0-1). Recent comparison of the Japanese and AJCC/UICC staging systems in 731 patients suggests that both are comparable. However, older studies suggest that the AJCC/UICC system more accurately estimates prognosis

4.13. TREATMENT

As with any cancer, treatment is adapted to fit each person's individual needs and depends on the size, location, and extent of the tumor, the stage of the disease, and general health. Cancer of the stomach is difficult to cure unless it is found in an early stage (before it has begun to spread). Unfortunately, because early stomach cancer causes few symptoms, the disease is usually advanced when the diagnosis is made. Treatment for stomach cancer may include surgery, chemotherapy, and/or radiation therapy. New treatment approaches such as biological therapy and improved ways of using current methods are being studied in clinical trials.

Surgery

Surgery is the most common treatment. The surgeon removes part or all of the stomach, as well as the surrounding lymph nodes, with the basic goal of removing all cancer and a margin of normal tissue. Depending on the extent of invasion and the location of the tumor, surgery may also include removal of part of the intestine or pancreas. Tumors in the lower part of the stomach may call for a Billroth I or Billroth II procedure.

Endoscopic mucosal resection (EMR) is a treatment for early gastric cancer (tumor only involves the mucosa) that has been pioneered in Japan, but is also available in the United States at some centers. In this procedure, the tumor, together with the inner lining of stomach (mucosa), is removed from the wall of the stomach using an electrical wire loop through the endoscope. The advantage is that it is a much smaller operation than removing the stomach. Endoscopic submucosal dissection (ESD) is a similar technique pioneered in Japan, used to resect a large area of mucosa in one piece. If the pathologic examination of the resected specimen shows incomplete resection or deep invasion by tumor, the patient would need a formal stomach resection.

Surgical interventions are currently curative in less than 40% of cases, and, in cases of metastasis, may only be palliative.

Chemotherapy

The use of chemotherapy to treat stomach cancer has no firmly established standard of care. Unfortunately, stomach cancer has not been particularly sensitive to these drugs, and chemotherapy, if used, has usually served to palliatively reduce the size of the tumor, relieve symptoms of the disease and increase survival time. Some drugs used in stomach cancer treatment have included: 5-FU (fluorouracil) or its analog capecitabine, BCNU (carmustine), methyl-CCNU (Semustine), and doxorubicin (Adriamycin), as well as Mitomycin C, and more recently cisplatin and taxotere, often using drugs in various combinations. The relative benefits of these different drugs, alone and in combination, are unclear. Clinical researchers have explored the benefits of giving chemotherapy before surgery to shrink the tumor, or as adjuvant therapy after surgery to destroy remaining cancer cells. Combination treatment with chemotherapy and radiation therapy has some activity in selected post surgical settings. For patients who have HER2 overexpressing metastatic gastric or gastroesophageal (GE) junction adenocarcinoma, who have not received prior treatment for their metastatic disease, the US Food and Drug Administration granted approval (2010 October) for trastuzumab (Herceptin, Genentech, Inc.) in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil). This was based on an improvement of the median overall survival (OS) of 2.5 months with trastuzumab plus chemotherapy treatment compared to chemotherapy alone (BO18255 ToGA trial). The combination of Herceptin with chemotherapy for treating metastatic gastric cancer was also sanctioned by the European regulatory authorities (2010 January). Doctors have also tested putting the anticancer drugs directly into the abdomen, often with warmed solutions of the medication (intraperitonealhyperthermicchemoperfusion).

Radiation

Radiation therapy (also called radiotherapy) is the use of high-energy rays to damage cancer cells and stop them from growing. When used, it is generally in combination with surgery and chemotherapy, or used only with chemotherapy in cases where the individual is unable to undergo surgery. Radiation therapy may be used to relieve pain or blockage by shrinking the tumor for palliation of incurable disease.

Multimodality therapy

While previous studies of multimodality therapy (combinations of surgery, chemotherapy and radiation therapy) gave mixed results, the Intergroup 0116 (SWOG 9008) study showed a survival benefit to the combination of chemotherapy and radiation therapy in patients with nonmetastatic, completely resected gastric cancer. Patients were randomized after surgery to the standard group of observation alone, or the study arm of combination chemotherapy and radiation therapy.

Those in the study arm receiving chemotherapy and radiation therapy survived on average 36 months; compared to 27 months with observation.

4.14. QUESTIONS FOR SELF-CONTROL

1. Define and explain the causes of gastric cancer.
2. What are the clinical symptoms of stomach cancer?
3. Enumerate the types of distant metastases generally associated with an advanced gastric cancer.
4. What are the indications for gastroscopy? Describe its importance in stomach pathologies.
5. Enumerate the types of surgeries used in gastric cancer.

4.15. TESTS FOR SELF-CONTROL

1. The most common histological type of stomach cancer is:
    a. Lymphoma
    b. Squamous cell cancer
    c. Adenocarcinoma
    d. Sarcoma
2. The most common site for gastric malignancies is:
    a. Antrum
    b. Cardia
    c. Body
    d. None of the above
3. Usually one of the earliest symptoms of gastric cancer is:
    a. Anorexia
    b. Weight loss
    c. An epigastric mass
    d. Postprandial abdominal heaviness
4. The optimal method of gastric cancer diagnosis is:
    a. MRI of abdomen
    b. Endoscopy with biopsy
    c. Fine-needle aspiration cytology
    d. PH-metry
5. The best results of surgery in gastric cancer cases are achived in:
    a. Patients with T2N2M0 tumours
    b. Patients with T1N0M0 tumours
    c. Patients with T3N0M1 tumours
    d. None of the above

Correct answers: 1c, 2a, 3d, 4b, 5b

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THEME 5

LIVER AND PANCREATIC CANCER

LIVER CANCER

5.1. EPIDEMIOLOGY

The annual number of worldwide liver cancer cases (626,000) closely resembles the number of deaths (598,000). Long-term survival rates are 3% to 5% in most cancer registries. The variable geographic incidence of liver cancer reflects the variable geographic incidence in HCV and HBV infections, which account for 75% of the world's cases. In Asia and Africa, high incidence rates have been associated both with high endemic HBV carrier rates as well as mycotoxin contamination of food, stored grains, drinking water, and soil. Ethnic factors also appear to be important because incidence rates can vary in the same population, according to ethnic origins. Ethnic Japanese in Japan have a higher incidence than those living in Hawaii, who in turn have a higher incidence than those living in California. Jews of European descent, when compared with Jews of African or Asian descent living in Israel, have a lower incidence. Differences have been found according to ethnic origin when examining an individual population. Los Angelinos of Japanese, Korean, and Chinese descent have a higher incidence of hepatoma than those of European or Hispanic descent.

HCC is 2.4 times more common in men than in women, and this difference is consistent globally. Higher levels of testosterone, lower levels of estrogens, and higher rates of liver disease are proposed explanations. In the United States, at all ages in both men and women, rates of HCC are two times higher in Asians than African Americans, which are two times higher than those in whites. There is a significant overall increase in the incidence of HCC in the United States during the past 25 years. This parallels the increase in HCV infection, the increase in immigrants from HBV endemic countries, and an increase in nonalcoholic fatty liver disease. The rate of increased incidence varies among different races in the United States. The widespread utilization of HBV vaccination is leading to a decrease in liver cancer in some areas. A dramatic demonstration of this is available from Taiwan, where HBV vaccine was introduced in 1984, and a reduction in the incidence of liver cancer was observed in children from 0.54 per 100,000 to 0.2 per 100,000 during a 16-year period.

5.2. ETIOLOGY, RISK FACTORS

Viral Hepatitis and Hepatocellular Carcinoma

Both case control studies and cohort studies have shown a strong association between chronic hepatitis B carriage rates and increased incidence of HCC. Beasley et al. Followed Taiwanese male postal carriers who were hepatitis B surface antigen (HBsAg) -positive and found an annual incidence of HCC of 495 per 1 00,000. This represented a 98 -fold greater risk than observed in HBsAg-negative individuals . By evaluating apparently asymptomatic HBsAg-positive blood donors at American Red

Cross centers, a minimum relative risk of 12.7 was noted for liver cancer compared with HBsAg-negative individuals. In men aged 30 to 35 years, three deaths due to HCC were noted, which relates to a 248-fold greater risk for such individuals compared with the general population.

HBsAg-positive individuals who are at greatest risk are those who are male, who have a family history of the disease, whose age is more than 45 years, and who have cirrhosis. Multivariate analysis has been used to determine " risk scores " for the development of HCCJ-9 Factors predictive of HCC include male gender, advanced age, specific promoter mutations, presence of cirrhosis, and higher viremia levels. If validated this may improve patient selection for surveillance.

Alcohol-Induced Hepatocarcinogenesis

There is a strong association between alcoholic cirrhosis and the development of HCC. Chronic alcohol consumption, by itself, has carcinogenic effects. Thus, chronic alcohol intake is known to lead to oxidative stress in the liver, inflammation, and cirrhosis . Ethanol is metabolized by alcohol dehydrogenases and cytochrome P-450, producing acetaldehyde and reactive oxygen species . Acetaldehyde binds directly to proteins and DNA. It damages mitochondria, initiating apoptosis. P-450 metabolism leads to reactive oxygen species, which lead to lipid consumption peroxidation, protein oxidation, and DNA adducts. Alcohol leads to monocyte activation and inflammatory cytokine production. This leads to activation of Kupffer cells, which release chemokines and cytokines, leading to hepatocyte necrosis. Oxidative stress has been demonstrated in alcoholic cirrhosis through increased isoprostane, a marker of lipid peroxidation. Oxidative stress promotes the development of fibrosis and cirrhosis, creating a permissive HCC microenvironment.

Oxidative stress may also lead to decreased STAT1-directed activation of IFNy signaling with consequent hepatocyte damage. However, it may simply be the effects of cirrhosis itself that lead to the development of HCC.

Other Etiologic Considerations

The 60 % to 8 0 % association of HCC with underlying cirrhosis has long been recognized, more typically with macronodular cirrhosis in Southeast Asia, but also with micronodular cirrhosis in Europe and the United States. Approximately 20% of U.S. patients with HCC do not have underlying cirrhosis, and probably not more than 70% have associated viral hepatitis. In addition to alcoholic cirrhosis and viral hepatitis, several underlying conditions have been found to be associated with an increased risk for the development of HCC.

These include autoimmune chronic active hepatitis, cryptogenic cirrhosis, metabolic diseases, and nonalcoholic fatty liver disease (NAFLD). NAFLD is the hepatic manifestation of the metabolic syndrome: obesity, insulin resistance, hypertriglyceridemia, and low high-density lipoprotein.

It is the most common liver disorder in the Western world. Increased free fatty acids in the liver leads to NFKB activation and inflammation. NAFLD can progress to cirrhosis and HCC.

Diabetes itself is associated with an increased risk of HCC. It is not clear whether this is related to insulin resistance, or perhaps the effects of diabetes-associated NAFLD, as previously described, or some other, as yet unknown, mechanism.

Several other metabolic diseases are also associated with an increased risk for the development of HCC. These include hemochromatosis (iron accumulation), Wilson disease (copper
accumulation), a rantitrypsin deficiency, tyrosinemia, porphyria cutanea tarda, glycogenesis types 1 and 3, citrullinemia, and orotic acid urea. In children, congenital cholestatic syndrome (Alagille syndrome) is associated with a familial type of HCC.

Chemical Carcinogens

Probably the best-studied and most potent ubiquitous natural chemical carcinogen is a product of the Aspergillus fungus, called aflatoxin B1 . Aspergillus flavus mold and aflatoxin product can be found in a variety of stored grains, particularly in hot, humid parts of the world, where grains such as rice are stored in unrefrigerated conditions. In the months following the monsoon in Southeast Asia, most village-based grains can be seen to be covered by a white layer that can easily be scraped off with the nails . This is highly enriched in aflatoxin and is consumed with the grain by most of the villagers over the following months. Data on aflatoxin contamination of foodstuffs correlate well with incidence rates of HCC in Africa and to some extent in China. In hyperendemic areas of China, even farm animals such as ducks have HCC.

Although some human medical compounds are hepatocarcinogens for rodents, there is little evidence that they play an important role in human hepatocarcinogenesis apart from sex hormones. There is considerable literature on the hepatocarcinogenicity of anabolic steroids as well as the induction of benign adenomas by estrogens. Although estrogens are capable of causing HCC in rodents, an epidemiologic association in humans has never been clearly shown. In an industrial society, a large number of environmental pollutants, particularly pesticides and insecticides, are known rodent hepatic carcinogens.

5.3. CLINICAL PRESENTATION

Common symptoms in patients affected with HCC include abdominal pain, weight loss, weakness, fullness and anorexia, abdominal swelling, j aundice, and vomiting. Common physical signs include hepatomegaly, hepatic bruit, ascites, splenomegaly, jaundice, wasting, and fever. There are some differences observed in presenting signs and symptoms between high- and low-incidence areas.

The most common symptom is abdominal pain, particularly in high-risk areas. An abdominal mass or swelling may also be noticed by patients. Abdominal swelling may occur as a consequence of ascites because of the underlying chronic liver disease or may be due to a rapidly expanding tumor. Occasionally, central necrosis or acute hemorrhage into the peritoneal cavity leads to death. Hemoperitoneum from bleeding HCC is also a potential complication of needle biopsy of highly vascular hepatomas. Weakness, malaise, anorexia, and weight loss are common reported symptoms that should trigger the consideration of a diagnosis of HCC in a known cirrhotic patient.

Jaundice is infrequent, and when present is usually the result of underlying liver disease. However, that can be attributed to the HCC in only 10% of patients presenting with jaundice. This may be because of obstruction of the main intrahepatic ducts, obstruction of the common hepatic duct at the porta hepatis, infiltration into the biliary radicals, or extremely rarely, blood in the biliary tree. Hematemesis may occur from esophageal varices from the underlying chronic liver disease with portal hypertension. Bone pain is seen in 3% to 12% of patients, but necropsies show pathologic bone metastases in approximately 20% of patients .

Respiratory symptoms may occur on presentation, but are rare. They are usually due to elevated hemidiaphragm consequent to hepatomegaly or pain from rib metastases. Pleural effusions may occur, but symptomatic lung metastases are rare. In countries where there is an active surveillance program, such as Japan, HCC tends to be identified at an earlier stage, when symptoms may be few or attributable only to the underlying disease.

Physical Signs

Hepatomegaly is the most frequent physical sign, occurring in 50% to 90% of the patients. The size of the liver may be massive, particularly in endemic areas. Abdominal bruits arising from the HCC, presumably from the associated vascularity, have a variable incidence, ranging from 6% to 25%. Ascites occurs in 30% to 60% of patients. It is usually due to the underlying liver disease, although occasionally it may be caused by hemoperitoneum. Splenomegaly occurs commonly, mainly due to the associated portal hypertension from the underlying liver disease. Acute splenomegaly may be due to portal vein occlusion by the tumor. Weight loss and muscle wasting are common, particularly with rapidly growing or large tumors. Fever is found in 10% to 50% of patients with HCC. The cause is not clear, although tumor necrosis has been invoked as an explanation. The signs of chronic liver disease may often be present, including j aundice, dilated abdominal veins, palmar erythema, gynecomastia, testicular atrophy, and peripheral edema.

The Budd- Chiari syndrome has been reported in several series because of HCC invasion of the hepatic veins . This causes tense ascites and a large tender liver. Virchow-Troisier nodes may occur in the supraclavicular region. Cutaneous metastases have also been reported as redblue nodules.

Paraneoplastic Syndromes

A variety of paraneoplastic syndromes have been described. Most of these are biochemical abnormalities without associated clinical consequences. The most important ones include hypoglycemia (also caused by end-stage liver failure) , erythrocytosis, hypercalcemia, hypercholesterolemia, dysfibrinogenemia, carcinoid syndrome, increased thyroxin-binding globulin, sexual changes (gynecomastia, testicular atrophy, and precocious puberty), and porphyria cutanea tarda. Hypoglycemia occurs in two settings. Relatively mild hypoglycemia occurs in rapidly growing HCC among the Chinese as part of a terminal illness. In the other setting, the HCC is more slowly growing, but the hypoglycemia may be profound. Its pathogenesis is unclear but may be related to production by the tumor of insulinlike growth factor-1. Erythrocytosis occurs in 3% to 12% of patients. Hypercholesterolemia may occur in 10% to 40% of patients. This has been shown to be due to an absence of normal feedback control in malignant hepatocytes and results from a deletion in 3-hydroxy-methylglutaryl coenzyme A reductase.

5.4. DIAGNOSTICS

History and Physical Examination

The history is important in evaluating putative predisposing factors, including a history of viral hepatitis or other liver disease, blood transfusion, alcohol abuse, or use of intravenous drugs. History should include a family history of HCC or hepatitis and detailed social history to include job descriptions for industrial exposure to possible carcinogenic drugs. Physical examination is important and should include examination of underlying liver disease such as j aundice, ascites, peripheral edema, spider nevi, palmar erythema, and weight loss. Evaluation o f the abdomen for hepatic size, presence of masses, hepatic nodularity, and tenderness, as well as presence of splenomegaly should be performed. Assessment of overall performance status is essential for management decisions.

Serologic Assays

The first serologic assay for detection and clinical follow-up of patients with HCC was AFP. It is found in the serum of animals bearing transplantable hepatomas and was later detected in humans. Improvements in this assay, including the development of radioimmunoassays for AFP, allowed sequential studies in high-risk patients and patients being treated either with surgical resection or chemotherapy.

Although AFP is elevated in approximately 70% of individuals from Asian countries bearing HCC, it is only increased in approximately 50% of patients from the United States and Europe. AFP-L3 is an abnormally glycosylated fraction of AFP that is lectin-bound and appears to be more specific for HCC.

The other most widely used assay is that for des-y-carboxy prothrombin protein induced by vitamin K abnormality (PIVKA-2). This protein is increased in as many as 80% of patients with HCC, but may also be elevated in patients with vitamin K deficiency. It may even have prognostic value. The elevations of both AFP and PIVKA-2 observed in chronic hepatitis and cirrhosis in the absence of HCC sometimes make it difficult to interpret these assays . Although many other assays have been developed, none have greater aggregate sensitivity and specificity Y-51.

Assessment of liver function is an important component of evaluation of the patient with HCC or suspected HCC, for treatment decision making and for assessment of prognosis.

The Child-Pugh classification of liver function, based on measurements of serum albumin, bilirubin, and prothrombin time, as well as presence or absence of ascites and encephalopathy, remains the most useful strategy for assessing liver function. Other tests such as isocyanine green retention and 99m-Tc GSA (diethylenetriamine-penta-acetic acid-galactosyl human serum albumin) scintigraphy have been investigated as more specific indicators of hepatic reserve in preparation for resection, but have not surpassed the Child-Pugh classification as a predictor of postoperative complications and liver failure. Assessment of portal pressure may be useful in evaluating patients prior to hepatic resection for HCC. Platelet count and white blood cell count decreases may reflect portal hypertension and associated hypersplenism. All patients should be tested for HBsAg and anti-HCV; if either test is positive, further confirmatory testing should be done including HBV DNA or HCV RNA.

Radiology

All HCC imaging techniques have improved considerably over the past few decades. High-resolution ultrasound (US) scans can detect liver lesions smaller than 1 cm, and is a useful creening tool. Fast multislice computed tomography (CT) and magnetic resonance (MR) scanners provide multiphasic contrastenhanced imaging, which is required for lesion characterization and to assess the locoregional extent, number, and size of the lesions, especially in a cirrhotic liver. HCCs can appear as solitary or multiple expansive or infiltrative masses. Expansive HCCs are well demarcated, nodular, and often encapsulated, while infiltrative HCCs have irregular margins and are often associated with invasion of the portal or hepatic veins. A mixed expansive and infiltrative growth pattern may also be seen.

HCC, unlike secondary liver metastases, has a propensity to invade to and grow within the portal vein, hepatic vein, inferior vena cava, and bile duct. To appropriately document the existence of HCC, a four-phase CT or MR imaging

(MRI) study is required: unenhanced, arterial, venous, and delayed phases. A characteristic feature of HCC is rapid enhancement during the arterial phase of contrast administration and "washout" during the later portal venous and delayed phases . The presence of arterial hypervascularity alone is insufficient for diagnosis of HCC, while the presence of venous washout is essential. Together, these findings are highly specific for HCC. Hepatic tumors are usually hypervascular, show tortuosity of the vessels, vascular pooling, and often demonstrate rapid entry of contrast into the associated hepatic veins. Arterial portal shunting in the presence of portal hypertension can also be observed. These shunts can be mistaken for HCC in a cirrhotic liver. Typical imaging findings of the nontumorous shunts include small, peripherally located, wedge-shaped enhancing lesions seen on arterial phase CT or MR scans; however, the shunts do not show negative enhancement compared with the adj acent liver parenchyma during the portal and delayed phases.

The primary questions that need to be addressed with HCC imaging studies are the location and number of lesions in the liver, whether they have typical features of HCC, whether there is evidence of extrahepatic tumor spread, and whether the vessels are patent or not. Because performance of imaging studies is critical to the diagnosis of HCC, it is recommended that all imaging studies be performed in expert centers.

Ultrasound

Ultrasonography screening in prospective studies has been shown to be more sensitive than repetitive AFP testing, especially for small tumors in high-risk patients. Using transducers of 3.5 or 5.0 MHz, both diagnosis and biopsy of suspicious lesions can be performed.

US is widely used in the diagnosis of HCC, particularly in surveillance programs for patients with chronic liver disease who are at risk for the development of HCC. The instrumentation is inexpensive and widely available. HCCs have variable echogenicity on gray-scale US. Expansive HCCs are usually seen as discrete nodules with a heterogeneous echo, and a hypoechoic rim may be present, corresponding to a fibrous capsule. Infiltrative HCCs also demonstrate heterogeneous echogenicity and can be missed on US scans. Arterial hypervascularity of HCCs can be better evaluated using power Doppler US with a microbubble contrast agent. Microbubblebased contrast agents are available for clinical use in Europe, Asia, and Canada, but not in the United States. HCCs typically show strong, heterogeneous enhancement with irregular intratumoral vessels on arterial phase scans. Portal and delayed scans
demonstrate negative enhancement, corresponding to "washout," and can diagnose portal venous thrombosis.

Computed Tomography Scans

The multislice, multiphasic (unenhanced, arterial, portal, and delayed phase) CT scan is the most commonly used standard imaging technique for determining the extent of HCC. Like US, it can miss lesions smaller than 1 cm, especially in the presence of cirrhosis.

The arterial phase scan demonstrates enhancement of hypervascular HCCs, and can also show hemodynamic changes associated with HCC or liver cirrhosis, such as arterioportal shunting. The portal phase scan is important for evaluation of venous invasion and distant metastases. The attenuation of HCCs on portal phase scans varies. A delayed-phase scan (at least 3 minutes after inj ection of contrast material) demonstrates negative enhancement of HCC (washout), compared with the adj acent liver parenchyma.

CT during arterial portography, in which contrast material is directly infused into the mesenteric vessels, and CT during hepatic arteriography have been shown to be superior to conventional dynamic CT in detecting very small lesions. However, direct comparisons of individual imaging modalities are limited by the lack of a gold standard to define the number and size of lesions identified and the rapidly evolving standard imaging techniques. Drawbacks of CT portography include the detection of small abnormalities that represent flow voids or benign lesions (pseudolesions) and false-negative findings, especially in instances in which there is fatty infiltration of the liver. These invasive CT procedures are infrequently performed because of their invasiveness.

Magnetic Resonance Scan

MRI is particularly good at detecting intrahepatic lesions, especially T2-weighted spin-echo sequences that are the most efficient for tumor detection. A nodule in a cirrhotic liver on T2-weighted images is highly suggestive of HCC; however, many well-differentiated HCCs may be seen as an isointensity or hypointensity. Some difficulty in distinguishing hemangiomas that have a very high T2 signal can be obviated because a less intense signal is observed with HCC.63 The signal intensity of HCC on T1-weighted MR scan varies with tumor grade. Larger HCCs tend to show more hypointensity than hyperintensity on T1-weighted imaging. Most borderline malignant lesions and the maj ority of well-differentiated HCCs show hyperintensity, partly due to fatty metamorphosis in HCCs. The fibrous capsule is seen as a hypointense rim on both T1- and T2-weighted images. Improvements of fast MRI techniques allow imaging of the entire liver in multiple phases of contrast enhancement. Multiphasic (unenhanced, arterial, portal, and delayed phases) gadolinium-enhanced T1-weighted imaging shows findings similar to those of multiphasic contrastenhanced CT and is important for detection and characterization of HCC, especially in a cirrhotic liver.

Delayed-phase MRI can help distinguish between intrahepatic cholangiocarcinoma and HCC, as intrahepatic cholangiocarcinoma does not show washout in the venous delayed phases.64 MRI with superparamagnetic iron oxide has been used to detect additional liver masses and can show higher diagnostic accuracy than multiphasic CT scan. The use of MRI angiography has also been reported in HCC.

Positron Emission Tomography

The role of [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET) scans in the valuation of HCC has been studied. In one retrospective study, FDG-PET imaging was successful in detecting only 64 % of lesions. Nevertheless, it had a clinically significant impact in 28% of patients above and beyond standard imaging, including the detection of unsuspected metastatic disease. A prospective comparison of triphasic CT, gadolinium-enhanced MRI, US, and FDG-PET was reported and verified by explanted liver specimens after transplant. This study revealed similar results for CT, MRI, and US, while none of the lesions were detected by PET imaging. At present, PET scans are not routinely used for staging or treatment decision making in HCC.

5.5. TNM-CLASSIFICATION

T – Primary Tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Solitary tumour without vascular invasion
T2 Solitary tumour with vascular invasion or multiple tumours, none more than 5 cm in greatest dimension
T3 Multiple tumours any more than 5 cm or tumour involving a major branch of the portal or hepatic vein(s)
T3a Multiple tumours any more than 5 cm
T3b Tumour involving a major branch of the portal or hepatic vein(s)
T4 Tumour(s) with direct invasion of adjacent organs other than the gallbladder *or* with perforation of visceral peritoneum

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M – Distant Metastasis

M0 No distant metastasis
M1 Distant metastasis

Group staging			
Stage	**T**	**N**	**M**
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

5.6. TREATMENT

Stage I and II HCC

Early-stage tumors can be managed successfully using a variety of techniques, including surgical resection, local ablation (radiofrequency ablation), and local inj ection therapies (ethanol injection) and transplantation. Because the maj ority of patients with HCC suffer from a field defect in the liver, they are at risk for multiple primary tumors throughout the liver in their lifetime. As discussed previously, the maj ority of patients will have significant underlying liver disease and may not tolerate maj or loss of hepatic parenchyma. Also, because of the underlying liver disease the patients may be eligible for liver transplantation in the future. Therefore, the most important principle to follow in early-stage HCC is to use treatment that allows for maximal sparing of the hepatic parenchyma. Avoiding maj or open surgery may also improve the results of
subsequent transplant surgery, if required.

Surgical Excision

Open surgical excision is a reliable method for treating stage I HCC with 5-year survival exceeding 50%. The goal is to obtain a 1-cm margin of normal tissue around the tumor. Beyond that requirement, the type of excision may not have an impact on cancer treatment outcome, although this is controversial. The excision of surface tumors may be best accomplished as a "nonanatomic wedge " excision, in which the tumor is simply excised with a 1 -cm margin and no more. The hepatic parenchyma can be divided using a variety of techniques, with the goal to minimize blood loss and maintain adequate exposure to ensure accurate margins are obtained. This can be performed safely for tumors up to 5 em in diameter with minimal blood loss. Deep tumors within the hepatic parenchyma and tumors greater than 5 em must be managed by an anatomic resection, where the most distal portal triad to the region involved by the tumor is controlled and the segment or segments are resected. Centrally located tumors may require a lobectomy and large tumors may require an extended hepatectomy.

The risk of maj or hepatectomy is high (5% to 10% mortality) because of the underlying liver disease and the potential for liver failure, but it is acceptable in selected cases. Preoperative portal vein occlusion can be performed to cause atrophy of the HCC-involved lobe and compensatory hypertrophy of the noninvolved liver. This allows for a safer resection. Intraoperative US is essential for planning the surgical approach for HCC. The US can image the proximity of major vascular structures that may be encountered during the dissection. For deep tumors, the US may identify the portal pedicle supplying the segment involved with HCC, and early control of this triad can be obtained. Intraoperative US is also essential for screening the rest of the liver for small tumors.

The utility of inflow occlusion (Pringle maneuver) in liver resection in patients with cirrhosis has been studied. Concern exists regarding whether ischemic inj ury to the liver will lead to liver failure or result in worsening cirrhosis. Numerous reports, including a randomized trial, have demonstrated no ill effects to inflow occlusion. In fact, the most significant predictor of postoperative mortality is blood loss, and the Pringle maneuver decreases blood loss, leading to an improvement in perioperative morbidity. The morbidity and mortality of a simple wedge excision should be minimal, but even slight manipulation of a cirrhotic liver may lead to liver failure and other complications, such as respiratory failure (acute respiratory distress syndrome, pneumonia), cardiovascular compromise, ascites, and infection. Cirrhotic patients are fragile with respect to the tolerance of any maj or surgery. Any significant postoperative complications may lead to liver failure. The Child-Pugh classification of liver failure is still the most reliable prognosticator for tolerance of hepatic surgery.

Only patients classified as Child-Pugh A should be considered for surgical resection and even then, those with significant portal hypertension may not tolerate surgery. Child-Pugh B and C patients with stage I HCC tumors should be referred for transplant, if appropriate. Patients with ascites or a recent history of variceal bleeding should be treated with transplantation.

As discussed previously, a variety of hepatic functional tests have been described for a quantitative assessment of hepatic reserve, but these techniques have not been adopted in routine practices. The most validated is the indocyanine green clearance test. Indocyanine green is delivered systemically and the hepatic retention is measured at 15 minutes. When the retention rate is less than 10% , all resections are possible. If 10% to 20%, a bisegmentectomy is well tolerated; if 20% to 29%, a single segment can be excised safely; if 30% or more, the risk of liver failure with any form of resection is high. In one study, the operative mortality was reduced to 1% using these criteria.

The risk of recurrence after adequate resection of HCC remains high (> 70% at 5 years). Predictors of recurrence include synchronous tumor sites and microvascular invasion. Surgical re-resection or salvage transplantation for HCC recurrence is seldom an option because of the aggressive, multifocal nature of this recurrence. Even Child-Pugh A cirrhotic patients or noncirrhotic patients may be better served with a less-invasive option than open excision. Although open surgical excision is the most reliable, the patient may be better served with a laparoscopic approach to resection, laparoscopic radiofrequency ablation, percutaneous radiofrequency ablation, or percutaneous ethanol injection. Minimizing the damage to normal parenchyma may improve the outcome and allow for all options in the future. No adequate comparisons of these different techniques have been undertaken to determine their relative success. In general, the choice of treatment is based on physician and patient preference.

Laparoscopic Resection

Laparoscopic surgical resection is a minimally invasive technique for resecting liver tumors. The abdomen can be insufflated with CO_2 or lifted with specialized retractors. Visualization is accomplished with a camera, and instruments are placed through the abdominal wall for hepatic parenchymal dissection. A laparoscopic approach to small, surface liver tumors is safe and feasible with widely available laparoscopic instruments. Larger lobectomies and segmentectomies are more commonly performed as a minimally invasive approach in major liver centers. Many centers have reported maj or laparoscopic hepatectomies with the proposed advantage of less morbidity and quicker recovery.

Laparoscopic surgical resection has the advantage over local ablative techniques of being able to assess margins pathologically, but has the same risk of bleeding, hepatic failure, and ascites as open excision. Laparoscopic surgery for cancer has the theoretical downside of spreading tumor cells at the time of laparoscopy. In general, surgeons have been reluctant to adopt laparoscopic approaches for cancer resection until randomized studies fail to demonstrate a negative impact on tumor recurrence compared with open surgery. Trials of more common procedures for cancer such as colectomies have not demonstrated a negative impact of the laparoscopic technique to date.136 This experience may translate to other procedures such as liver resection as long as the same oncologic principles of resection are used with the laparoscopic approach as they are with the open approach.

Local Ablation Strategies

Radiofrequency ablation is a technique that uses heat to thermally ablate tumors. A thin probe (18 gauge) is inserted into the middle of a tumor, then needle electrodes are deployed to adjustable distances . An alternating electrical current (400 to 500 kHz) is delivered through the electrodes.

The current causes agitation of the particles of the surrounding tissues, generating frictional heat. The heat leads to a reliable sphere of necrosis. The size of the sphere depends on the length of deployment of the electrodes. Currently, the maximum size of the probe arrays allows for a 7-cm zone of necrosis . This would be adequate for a 5-cm tumor. The heat reliably kills cells within the zone of necrosis. The lack of uniform success is because of the difficulty of positioning the probe accurately in three dimensions using US or CT guidance. Also, large blood vessels may act as heat sinks, preventing adequate cytodestruction of cells adj acent to these structures. Finally, treatment of tumors close to the main portal pedicles can lead to bile duct injury and obstruction. This limits the location of tumors that are optimally suited for this technique.

In case series examining the results of treatment of HCC with radiofrequency ablation, the data suggest a uniformly excellent response, with a local recurrence rate (at the site of ablation) of between 5% and 20%. The treatment can be performed percutaneously with CT or US guidance, or at the time of laparoscopy with US guidance.

The downside of the laparoscopic approach is the requirement for general anesthesia, but some have suggested better results with this approach.

The percutaneous approach may also be limited by structures at risk for injury around the tumor, such as the diaphragm, colon, or gallbladder. These structures can be retracted free with a laparoscopic approach. In general, radiofrequency ablation is reliable as a single treatment. A single ablation can take up to 20 minutes for a 7-cm ablation. It is well tolerated and can be performed as an outpatient procedure. It can be repeated numerous times, especially if performed percutaneously. This technique is best suited overall to small tumors (<3 cm) deep within the hepatic parenchyma and away from the hepatic hilum.

Complete preservation of hepatic parenchyma is possible with reliable tumor killing. A theoretical risk of needle tract tumor seeding exists. The track can be thermally ablated while retracting the needle, which decreases this risk.

Local Injection Therapy

Numerous agents have been used for local injection into tumors, but the most widely used agent has been absolute ethanol. Ethanol injection into HCC is the most widely used therapy worldwide. The relatively soft HCC within the hard background cirrhotic liver allows for injection of large volumes of ethanol into the tumor without diffusion into the hepatic parenchyma or leakage out of the liver. Ethanol causes a direct destruction of cancer cells, but it is in no way selective for cancer, and will destroy normal cells in the vicinity. The key to success is the accuracy of the injection. This technique is associated with a 15% risk of recurrence at the site of treatment. It has the advantage of being minimally invasive-a very small needle can be used for inj ection-and it is quite inexpensive.

The disadvantage is that a response usually requires multiple injections (average, three). The maximum size of tumor reliably treated is 3 cm, even with multiple injections. For this reason, radiofrequency ablation is preferable to most clinicians. Also, randomized trials have suggested an improved survival for radiofrequency ablation compared with percutaneous ethanol injection.

Nevertheless, the cost of radiofrequency ablation may be prohibitive in many places. Acetic acid is another agent with established success as a local inj ection for HCC. A randomized trial suggested that local recurrence is improved with acetic acid compared to ethanol.

Transplantation

A viable option for stage I and II tumors in the setting of cirrhosis is liver transplantation. The expected morbidity and mortality for transplantation for non-cancer-related liver disease has improved with appropriate patient selection and established expertise of liver transplant programs. With this acceptable morbidity and mortality, the maj or considerations for liver transplantation become the long-term outcome in terms of cancer recurrence.

The National Institutes of Health Consensus Conference on liver transplantation in 1983 concluded that primary hepatic malignancy confined to the liver but not amenable to resection may be an indication for ransplantation, although it was noted that the results had indicated a strong likelihood of recurrence of the malignancy. As predicted, recurrence proved to be the rule rather than the exception, and results were dismal. As survival data gradually accumulated, advanced HCC cases were abandoned. However, no consensus existed among transplant surgeons and physicians as to the acceptable limits of HCC for which transplant could be beneficial, leaving each program's personnel free to transplant any patient it deemed deserving.

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Stage III and IV Tumors

Fewer surgical options exist for stage III tumors involving maj or vascular structures. In patients without cirrhosis, a major hepatectomy is feasible and provides the best chance of long-term survival, although prognosis is poor. Patients with Child-Pugh A cirrhosis may be resected, but a lobectomy is associated with significant morbidity and mortality, and long-term prognosis is poor. Nevertheless, a small percentage of patients will achieve long-term survival, justifying an attempt at resection when feasible. Preoperative portal vein occlusion in order to induce compensatory hypertrophy preoperatively may improve the results or help define which patients will tolerate a major hepatectomy. Because of the advanced nature of these tumors, even successful resection will be met with rapid recurrence.

These patients are not considered candidates for transplantation because of the high tumor recurrence rates, unless their tumors can be downstaged with adjuvant therapy. Although unproven, these patients are ideal for neoadj uvant treatment approaches, such as embolization.

Decreasing the size of the primary tumor allows for less surgery, and the delay in surgery allows for extrahepatic disease to manifest on imaging studies and avoid unnecessary surgery on the primary tumor. Successful regional therapy strategies may make the patient eligible for transplantation.

The prognosis is poor for stage IV tumors, and no surgical treatment is recommended. Care must be taken to differentiate multifocal disease from intrahepatic metastases, as the latter has a much worse prognosis. Molecular genotyping may be the best way to make this differentiation.

Radiation Therapy

Retrospective phase 1 and phase 2 studies have shown that tumoricidal doses of radiation therapy can be delivered safely to a wide spectrum of HCCs (early stage and locally advanced with portal vein thrombosis) using a variety of strategies. Although the potential for long-term tumor control has been demonstrated in selected patients, randomized trials are required to help define the role of radiation therapy in the management of HCC. The low tolerance of the whole liver to irradiation limited the early application of radiation as a treatment for liver cancer.

The first hepatic toxicity observed following liver irradiation was referred to as radiation-induced liver disease (RILD), a syndrome of anicteric ascites, hepatosplenomegaly, and elevated alkaline phosphatase, seen within 3 months following irradiation.

Pathologically, RILD is characterized by congestion of the central veins and central lobular sinusoids, followed by epithelial cell proliferation in the central lobulars zone, hepatocyte atrophy, and fibrosis. Proinflammatory cytokines such as transforming growth factor-/31 and interleukin-6 have been implicated in its development. Elevation of transaminases, thrombocytopenia, variceal bleeding, and general decline of liver function have also been observed, most often in patients with cirrhosis. Reactivation of hepatitis B may occur because of interleukin-6 released by irradiated endothelial cells. Changes in CT and MRI contrast enhancement and perfusion are seen within regions of the liver irradiated to high doses.

Brachytherapy

Although interstitial and intraluminal brachytherapy have been used to treat liver metastases and cholangiocarcinoma, there is less experience in HCC perhaps because of the increased risk of intrahepatic hemorrhage in patients with underlying cirrhosis. Intraluminal iridium-192 has been used for intraductal HCC and following incomplete resection.

Regional Chemotherapy

A large number of encouraging reports have appeared concerning a variety of regional chemotherapies for HCC confined to the liver. Much of the experience has come from Europe and Asia, where a large number of cases have allowed systematic studies to be performed. Despite the fact that increased hepatic extraction of chemotherapy has been shown for very few drugs, some drugs such as cisplatin, doxorubicin, mitomycin C, and others have been found to produce substantial objective responses when administered regionally. In contrast to the Western experience of metastatic colon cancer to the liver, few data are available on continuous hepatic arterial infusion for HCC, although recent pilot studies are suggestive. Almost all studies have been done using bolus administration. Because almost none of the reports have stratified responses or survival based on TNM staging, it is difficult to know long-term prognosis in relation to tumor extent.

Many, but not all, of the studies on regional intrahepatic arterial chemotherapy also use an embolizing agent such as lipiodol, gelatin (Gelfoam), starch (Spherex), microspheres, or polyvinyl alcohol (Ivalon). The last is rarely used now because of increased hepatotoxicity.

Most centers in the United States now use commercially available degradable starch microspheres of defined size ranges. Consistently higher obj ective response rates appear to be reported for arterial administration of drugs together with some form of hepatic artery occlusion, compared with any form of systemic chemotherapy to date. The widespread use of some form of embolization (e.g., TACE) in addition to chemotherapy has added to its toxicities. These include the almost universal presence of high fever (>95%), abdominal pain (>60%), and anorexia (>60%). In addition, more than 20% of patients have increased ascites or transient elevation of transaminases. Cystic artery spasm and cholecystitis are also not uncommon. Several studies have examined responses and survival, using mixtures of both chemotherapy and transhepatic arterial embolization o r occlusion. Several studies have compared intrahepatic arterial chemotherapy, usually with addition of lipiodol and Gelfoam embolization, to either untreated controls or to embolization (with or without chemotherapy) or to other chemotherapy. All of these studies used either doxorubicin or cisplatin at rather low doses when compared with what is employed systemically. None of the studies yielded response rates greater than 50%. As a consequence, few of these studies showed any survival advantage. Nonrandomized studies reported higher responses to platinum or showed greater survival, but only when compared with historical controls. One study showing promising survival figures suggested decreased postresection recurrences. The hepatic toxicities associated with embolization have been ameliorated by the use of degradable starch microspheres, with 50% to 60% response rates.

Similar results were achieved in a randomized study of doxorubicin and cisplatin with or without lipiodol or with doxorubicin and Gelfoam. Because there is no standard chemotherapy drug for HCC, combinations are used differently by different groups and often at suboptimal doses. The best strategy now is to take one step backward and find the optimum intra-arterial doses for each of our probable two current best drugs, cisplatin and doxorubicin, and then to combine a single drug at optimal dosing with an arterial-occluding agent. Once regimens that reliably and consistently induce more than 50% partial responses are available, effects on survival should be detectable.

In addition, different studies report noncomparable patients. Tumor stage has been rarely given, so that different studies report responses of patients with differing tumor burdens and degrees of cirrhosis. Other reports have questioned the value of any chemotherapy added to embolization because of the lack of apparent survival advantages. A high percentage of HCC patients die of their cirrhosis and not of their tumor. A reasonable target now should be to improve patient survival and quality of life, with or without higher tumor response rates. In addition, it is not clear that the formal CT response criteria of oncologic partial responses are adequate for HCC. It appears that a loss of vascularity seen on CT without size change is also a reasonable index of loss of viability and thus tumor response to occlusion. Several studies have compared intrahepatic arterial chemotherapy, usually with addition of lipiodol and Gelfoam embolization, to either untreated controls or to embolization (with or without chemotherapy) or to other chemotherapy. All of these studies used either doxorubicin or cisplatin at rather low doses when compared with what is employed systemically. None of the studies yielded response rates greater than 50%. As a consequence, few of these studies showed any survival advantage. Nonrandomized studies reported higher responses to platinum or showed greater survival, but only when compared with historical controls. One study showing promising survival figures suggested decreased postresection recurrences.

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A phase 2 study of GEMOX combined with bevacizumab, a monoclonal antibody inhibitor of VEGF ligand, in 33 patients resulted in a 20% partial response rate a n d a median survival of 9.6 months. Bevacizumab has also been investigated in other phase 2 studies. One multi-institutional phase 2 study found 1 and 2-year survival rates of 53% and 28%, respectively, with serious bleeding occurring in 11% of patients. TSU-68, an oral antiangiogenesis compound that blocks VEGFR-2, plateletderived growth factor receptor, and fibroblast growth factor receptor, has been studied in a phase 1/2 study in Japan. A phase 2 study of erlotinib, a receptor tyrosine kinase inhibitor with specificity for epidermal growth factor receptor, demonstrated a 9% response rate and median survival of 13 months.

Bevacizumab and erlotinib have been studied in another phase 2 study, with a median survival of 68 weeks and median progression-free survival of 39 weeks. A phase 2 study of sorafenib, an oral multikinase inhibitor that has activity against Raf-1, B-Raf, VEGFR2, DGFR, c-Kit receptors, and other receptor tyrosine kinases, was performed in 137 patients with advanced HCC. The partial response rate was poor, 2.2% , yet the time to progression was 5.5 months, and median overall survival was 9.2 months, providing the basis for the SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) randomized trial. The SHARP trial was performed in 602 patients with advanced, predominantly hepatitis C-related, Child-Pugh A, HCC and demonstrated a survival advantage for sorafenib (n = 299) versus placebo (n = 303).

There was a 31% decrease in the risk of death, with a median survival of sorafenib and placebo arms of 10.7 months and 7.9 months, respectively (P=0.00058). Sorafenib was also associated with a significant improvement in time to progression from 2.8 months for placebo to 5.5 months for sorafenib. Serious (grade 3 and 4) adverse events of diarrhea and hand-foot syndrome were more frequent with sorafenib (11% vs. 2% and 8% vs. 1%, respectively). Discontinuation of sorafenib because of adverse events occurred in 15% of patients. A second randomized trial conducted in Asia of predominantly hepatitis B patients confirmed a comparable hazard ratio for a survival benefit, but with substantial lower absolute benefit.

In summary, sorafenib is established as the first-line treatment in patients with advanced HCC unsuitable for other established local and regional therapies.

PANCREATIC CANCER

5.7. EPIDEMIOLOGY

An estimated 232,000 people were diagnosed worldwide with pancreatic cancer in 2002, with 227,000 people dying from the disease in that same year. Although pancreatic cancer ranks as the 13th most common type of cancer worldwide, it is the eighth most common cause of cancer-related death. The greatest impact on cancer-related deaths is in developed countries where pancreatic cancer is the fifth leading cause of cancer-related death after lung, stomach, colorectal, and breast cancers. In developed countries the incidence and mortality rates range from 7 to 9 per 100,000 for men and 4.5 to 6 per 100000 for women. In Europe 64,000 people died from pancreatic cancer in 2006, representing 5.5% of cancer-related deaths, the fifth leading cause of cancer mortality. In the United States, there were an estimated 42,470 new cases of pancreatic cancer in 2009 with approximately 35,240 deaths, the fourth most common cause of cancer-related death. The lifetime risk of an American developing pancreatic cancer is 1.32% (95% incidence for the entire population of 11.4 per 100,000; this has not changed over the past 10 years studied (1995 to 2004).

Of patients with available data in the United States diagnosed with pancreatic cancer in the years 1996 to 2004, less than 10% presented with local disease, 26% with regional disease, and over half had distant metastases. The incidence of pancreatic cancer is lower in developing countries, which may be a reflection of lifespan and diagnostic limitations. Among the developing countries, the incidence is highest in Central and South America. Pancreatic cancer tends to occur later in life. Only 10% of patients in Europe present before the age of 50, while those aged 50 to 54 experience an incidence of 9.8 per 100,000, and those 70 to 74, an incidence of 57 per 100,000. The median age of diagnosis with pancreatic cancer in the United States is 72, with less than 13% of cancers diagnosed prior to the age of 55 and greater than 69% of cancers diagnosed after the age of 65. Although the peak incidence is later in life, pancreatic cancer is the third leading cause of cancer-related death in the United States for those aged 40 to 59. In the United States, blacks experience a higher rate o f pancreatic cancer than whites, with an annual incidence of 16.7 per 100,000 versus 10.9 per 100,000, respectively. Death from pancreatic cancer is similarly elevated, with an annual rate of 14.6 per 100,000 versus 10.6 per 100,000.

Diagnosis is slightly but significantly earlier in African Americans, with a median age of diagnosis of 68 compared to median age of diagnosis of 73 for whites. In contrast, persons of nonwhite Hispanic/Latino descent and persons of Native American ancestry do not have disparate incidence of pancreatic cancer compared to persons of European descent, although these groups do differ in other cancer types.

Five-year survival from all stages of disease is 5%, which is a statistically significant increase from the 2% survival rate in 1975 to 1977. However, the long-term survival rate often dissipates when examined carefully.

Carpelon-Holstrom et al. examined the records of 4,922 pancreatic cancer patients registered in the Finnish Cancer Registry from 1990 to 1996 and found 89 subjects who were 5-year survivors. Pathology was reviewed on all 89 subjects. In 59 cases, the diagnosis was found to be a histology other than pancreatic ductal adenocarcinoma, and 20 cases carried a clinical or cytological diagnosis or did not have pathology available for analysis. Only ten cases of long-term survival from pancreatic ductal carcinoma could be confirmed.

5.8. ETIOLOGY, RISK FACTORS

Tobacco

Tobacco smoke exposure plays a significant role in the development of pancreatic adenocarcinoma. It has been estimated that tobacco smoking contributes to the development of 20% to 30% of pancreatic cancers. The strongest associations between cigarette smoking and pancreatic cancer have been observed when the pack years smoked were within the previous 10 years. Importantly, smoking cessation can reduce this risk, which in one study approached that of a never-smoker after 5 years of smoking cessation.

Environmental tobacco smoke (ETS) contains the same toxins, irritants, and carcinogens, such as carbon monoxide, nicotine, cyanide, ammonia, benzene, nitrosamines, vinyl chloride, arsenic, and hydrocarbons, as primary cigarette smoke. Pancreatic cancer risk is increased particularly among neversmokers exposed to ETS in childhood and to a lesser extent, at work or home during adulthood. Similar findings come from a prospective cohort in the Nurses' Health Study showing an increased risk of pancreatic cancer among women having ETS exposure from maternal smoking, but not paternal smoking. This implies ETS exposure i n utero or early life may result in pancreatic cancer in adulthood. More recently, the role of smokeless tobacco in pancreatic cancer development has been suggested. Other studies, including one supported by a tobacco company, claim that more rigorous methodol ogy refutes these findings. Nevertheless, investigators have demonstrated the presence of known carcinogens in three of the five most popular brands of moist snuff sold in the United States.

Infectious Diseases

Previous reports have suggested an association between Helicobacter pylori and pancreatic cancer. More recently, investigators performed a population- based, case-control study and found an association between risk of pancreatic cancer, H. pylori colonization, and ABO blood groups. Likewise, hepatitis B may also be a risk factor for pancreatic cancer. In a recent study involving 476 patients with pathologically confirmed adenocarcinoma of the pancreas and 879 age-, sex-, and race-matched healthy controls, a possible association between past exposure to hepatitis B virus (HBV) and pancreatic cancer was discovered.

The proximity of the liver to the pancreas and the fact that the liver and pancreas share common blood vessels and ducts may make the pancreas a potential target organ for hepatitis viruses. This is supported by the discovery of hepatitis B surface antigen (HBsAg) in pure pancreatic j uice and pure bile juice.

Occupational Factors

A meta-analysis of 20 population studies of occupational exposures and pancreatic cancer from journal publications during the period 1969 to 1998 showed exposure to chlorinated hydrocarbon solvents, nickel and nickel compounds, chromium compounds, polycyclic aromatic hydrocarbons, organochlorine insecticides, silica dust, and aliphatic solvents conveyed elevated risk ratios. Overall, the occupational etiologic fraction for pancreatic cancer was estimated at 12%, but it increased to 29% when the chlorinated hydrocarbon solvents were considered in a subpopulation. Elevated serum levels of organochloride compounds (dichlorodiphenyltrichlorethane, dichlorodiphenyldichloroethylene, and polychlorinated biphenyls) are also associated with the development of pancreatic cancer. Approximately 90% of pancreatic cancer patients have an acquired K-ras oncogene mutation. In a case-control study, pancreatic cancers with K-ras mutations had significantly higher levels of organachloride compounds compared to cancers without the K-ras mutation and to those in the control group.

These compounds are postulated to enhance the actions of K-ras rather than cause the mutation, suggesting a gene-environment interaction or effect modification.

Demographic and Host Risk Factors

A number of demographic risk factors have been associated with the development of this disease worldwide. These include older age (most cancers occur between the ages of 60 and 80), African American race, low socioeconomic status, and Ashkenazic Jewish heritage (related to germline mutations). Host etiologic factors associated with an increased risk of pancreatic cancer include a history of diabetes mellitus, chronic cirrhosis, pancreatitis, a high-fat or cholesterol diet, and prior cholecystectomy.

Diabetes Mellitus

Diabetes mellitus (DM) has been implicated as both predisposing to pancreatic cancer and a manifestation of the malignancy. Two meta-analyses have shown that pancreatic cancer occurs with increased frequency in patients with longstanding diabetes (diagnosed at least 5 years prior to the diagnosis of pancreatic cancer or death due to pancreatic cancer). In contrast, a cohort study from Sweden found an increased risk of the diagnosis of pancreatic cancer after an initial hospitalization for diabetes that persisted for more than a decade but decreased with the duration of diabetes. Although not uniformly accepted, it is estimated that DM doubles the risk of pancreatic cancer.

Although longstanding diabetes mellitus appears to be a risk factor for pancreatic cancer, some studies also suggest new-onset diabetes as a potential manifestation. Ductal adenocarcinoma can induce peripheral insulin resistance. Furthermore, a putative cancer-associated diabetogenic factor has been isolated from conditioned medium of pancreatic cancer cell lines and patient serumP The existence of such a factor is further supported by clinical observations showing diabetes can resolve after surgical resection of the primary tumor.

Obesity, Physical Activity, and the Metabolic Syndrome

High body mass index (a measure of obesity), increased height, and a low level of physical activity all increased the risk of pancreatic cancer, as demonstrated in a cohort study of 160,000 health professionals. Moderate physical activity resulted in decreased pancreatic cancer rates, and merely walking or hiking 1.5 hours or more per week was associated with a 50% reduction in pancreatic cancer, independent of smoking cessation. Further evidence for a link between obesity, insulin resistance, and pancreatic cancer comes from emerging recognition of the metabolic syndrome. While definitions vary, this syndrome is characterized by type II DM, truncal obesity, hypertension, and dyslipidemia, which together increase the risk of cardiovascular disease. More recent epidemiologic data have suggested the metabolic syndrome as a risk factor for pancreatic cancer. Of note, fatty infiltration of the pancreas may lead to steatopancreatitis, suggesting a potential link between obesity, nonalcoholic fatty pancreatic disease, nonalcoholic steatopancreatitis, and pancreatic cancer.

Pancreatitis

Although an association between pancreatitis and an increased risk of pancreatic cancer has long been suspected, the magnitude of the risk remains uncertain. Older clinical studies suggested that chronic forms of pancreatitis were most closely associated with the development of pancreatic cancer. In contrast were the findings of Karlson et al., who found that the standardized incidence ratio (observed/expected) for the development of pancreatic cancer was increased in patients with pancreatitis (2.8; 95%CI, 2.5 to 3.2), after 10 years or more, the excess risk declined and was of borderline significance.

The incidence of p ancreatic adenocarcinoma is also increased in patients with hereditary pancreatitis or tropical pancreatitis. Hereditary pancreatitis has an autosomal dominant pattern of transmi ssion with 80% penetrance. Symptoms usually arise by age 40 years, but can occur before age 5 years, and the cumulative risk of developing pancreatic cancer by age 70 in patients with hereditary pancreatitis has been estimated to be 40%.

Inflammation and Pancreatic Cancer

No matter what the underlying cause, results from several sources detailed above implicate inflammation as a potential driver of pancreatic carcinogenesis. Whether the insult is precipitated by an infectious agent, results from steatopancreatitis related to obesity or the metabolic syndrome, or pancreatitis secondary to alcohol or genetic predisposition, preclinical and epidemiologic studies suggest inflammation as a central mediator of the neoplastic process.

Genetic Predispositions

Genetic predisposition plays a small but significant role in pancreatic cancer risk. Mutation and constitutive activation of the oncogene K-ras is present in approximately 95% of all pancreatic cancer with frequent inactivation of several tumor suppressor genes (p53, DPC4, p16, and BRCA2). Nearly 90% of all cases have p16 mutations, 55% to 75% have p53 mutations, and 50% have DPC4 mutations. The frequency of DNA repair gene inactivations, which include BRCA2, MLHl, FANC-C, and FANC-G, is relatively low.

It is estimated that 10% to 20% of pancreatic cancers are hereditary or have a familial link. Multiple lines of evidence support this. Cohort studies have shown an increased risk of developing the disease among individuals who report a family history of pancreatic cancer. Tersmette et al have shown that this risk increases with the number of affected members in the family. An 18-fold increased risk was found in familial pancreatic cancer kindreds compared to sporadic groups. When three or more family members were affected, there was a 57-fold increased risk.

Data from Familial Pancreas Tumor Registries: PALB2 Germline Mutations

The vast maj ority of cases in which there is a familial aggregation of pancreatic cancer are not explained by known genetic syndromes . The National Familial Pancreas Tumor Registry has therefore been established at the Johns Hopkins Medical Institutes (JHMI) with the hope of identifying the causes for the aggregation of pancreatic cancer in families.

Early analyses of the kindreds enrolled in the registry showed that the risk of cancer is 18-fold greater in firstdegree relatives of familial pancreatic cancer cases and also extends to second-degree relatives. Rates of pancreatic cancer are higher among second-degree relatives of familial cases compared with sporadic pancreatic cases (3.7% vs. 0.6%; $p<0.0001$). More recently, the Hopkins group has identified mutations in the PALB2 gene in 3 of 96 patients with familial pancreatic cancer (3.1%), defined as having at least one first-degree relative with pancreatic cancer.40 These mutations each produced a different stop codon in the protein-coding regions of the gene. Shortly thereafter, other investigators interrogated European familial pancreatic cancer registries for PALB2 mutations among index cases. Three index patients from 81 families (3.7%) harbored truncating mutations within the exons of the PALB2 gene.

Of note, these three families also had a family history of breast cancer. Thus, traditional family registries, coupled with increasingly sophisticated genetic analyses, can be expected to identify novel germline mutations that drive pancreatic carcinogenesis.

Inherited Syndromes

Although accounting for less than 20% of the familial aggregation of pancreatic cancer, several genetic syndromes (caused by germline mutations) associated with an increased risk of pancreatic cancer have been identified. They include:

1. Familial breast cancer with germline mutations in the BRCA2 gene. Carriers of germline BRCA2 mutations have a 3.5- to 10-fold increased risk of developing pancreatic cancer, and 17% (one in six) of patients with pancreatic cancer and a strong family history (at least three family members with pancreatic cancer) have been shown to have germline BRCA2 mutations. BRCA2 mutation is the most common germline mutation in patients with hereditary pancreatic cancer.

2. Familial atypical multiple mole melanoma syndrome with germline mutations in the p16 gene. Carriers of p16 germline mutations have a 12- to 20-fold increased risk of developing pancreatic cancer, as well as an increased risk of melanoma.

3. The Peutz-Jeghers syndrome, characterized by mucocutaneous melanocytic macules and hamartomatous polyps of the gastrointestinal tract. Patients with the Peutz-Jeghers syndrome have a greater than 100-fold increased risk of developing pancreatic cancer.

4. The hereditary nonpolyposis colorectal cancer syndrome, characterized by germline mutations in one of the DNA mismatch repair genes (hMSH1, hMSH2, etc.).

5 . Hereditary pancreatitis with germline mutations in the PRSSl (cationic trypsinogen) gene. Patients develop severe pancreatitis at a young age (often affects children and adolescents) and have a 50-fold excess risk of developing pancreatic cancer.

6. Ataxia-telangiectasia, a rare autosomal recessive inherited disorder, characterized by cerebellar ataxia, oculocutaneous telangiectasias, and cellular and humoral immune deficiencies . The gene, ATM, is also associated with an increased risk of leukemia, lymphoma, and cancers of the breast, ovaries, biliary tract, stomach, and, occasionally, the pancreas.

7. Pancreatic cancer, pancreatic insufficiency, and DM have been described in a family (called Family X), and the phenotype has been linked to chromosome 4q32-34.

5.9. SCREENING

Currently, no proven screening strategies exist for pancreatic cancer. But there is intense study into developing methods of early detection because cancer of the pancreas has curative potential in the setting of PaniN and small invasive ductal adenocarcinomas, which are amenable to surgical resection. For example, Japanese investigators compiled data for patients with early cancers, finding patients (n=36) with resected tumors less than 1.0 cm in size experienced a 57% 5-year survival.

Unfortunately, early diagnosis is quite uncommon. Prevalence of the disease is too low in the general population for screening with currently available techniques. Recent efforts in screening have focused on individuals considered to be at high risk for pancreatic cancer, such as those belonging to a familial pancreatic cancer kindred or having a known genetic syndrome. Others have suggested that obese patients diagnosed with diabetes over the age of 60 may also be appropriate candidates for pancreatic cancer screening. In general, pancreatic cancer screening has relied on endoscopic ultrasonography (EUS), which allows for excellent visualization of the gland and detection of subtle changes in pancreatic architecture. Although multidetector dynamic-phase computed tomography (CT) imaging has been improving in resolution, EUS maintains its advantage in detecting small abnormalities (less than 1 cm) within the pancreas. In addition, EUS-guided fine-needle aspiration (FNA) may provide a cytologic diagnosis for lesions measuring 2 to 5 mm.

5.10. CLINICAL PRESENTATION

The clinical presentation of pancreatic cancer is often dependent on the location of the tumor within the gland, with most symptoms initially appearing vague and nonspecific. The majority of pancreatic tumors develop in the head or uncinate process, putting the intrapancreatic portion of the bile duct at risk for obstruction. Jaundice is, therefore, a common presenting symptom and may be preceded by episodes of biliary colic, anorexia, or vague gastrointestinal distress.

Some tumors of the pancreatic head or body will not involve the bile duct but may invade the duodenum or neural structures, including the celiac or mesenteric plexi. Such invasion results in pain that may be characterized by aching, pressure, or burning. The presence of pain may have implications for operative treatment. In a prospective study conducted at Memorial Sloan-Kettering Cancer Center (MSKCC), pain, pain intensity, and location were evaluated among 77 patients appearing to have resectable pancreatic cancer. The presence of pain prior to exploratory laparotomy was a predictor of unresectable tumor and the presence of metastatic disease. Moreover, for those patients undergoing surgery with curative intent, the presence of pain prior to surgery was associated with a worse survival (9.2 months vs. 21.9 months; P=0.045).

This implicates pain as a sign of more advanced disease, even when imaging suggests the primary tumor is potentially resectable. Pancreatic exocrine insufficiency manifested by steatorrhea occurs relatively infrequently as a presenting symptom, and while it is often initially mild and easily manageable, it may worsen after surgical resection or radiation therapy. Pancreatic ductal obstruction may lead to acute pancreatitis, which is occasionally a presenting sign of pancreatic cancer. When a patient without risk factors for pancreatitis experiences an acute attack, an underlying pancreatic cancer should be considered and thoroughly investigated. Importantly, it is increasingly recognized that glucose intolerance or overt DM is present in up to 70% of patients diagnosed with pancreatic cancer, and when diabetes develops in an older adult or when it is found in conjunction with other symptoms such as pain, anorexia, or weight loss, the possibility of an underlying pancreatic neoplasm should be raised.

Other symptoms of pancreatic cancer include superficial or deep venous thromboses, anorexia, or weight loss. In some studies, weight loss is the most common symptom of pancreatic cancer. Unfortunately, initial symptomatology, to include weight loss, may be indicative of metastatic disease, such as night sweats, significant fatigue, or liver pain. Gastric outlet obstruction, increasing abdominal girth from ascites, and skin manifestations all occur in pancreatic cancer, but are fairly uncommon as presenting signs and symptoms.

5.11. DIAGNOSTICS

The initial goals in the approach to the symptomatic patient are to confirm the diagnosis of a pancreatic mass, reestablish biliary tract patency, determine the extent of disease, determine the resectability of the primary tumor, and establish a histologic diagnosis. History, physical examination, and noninvasive and minimally invasive imaging often can accomplish all of these goals.

Physical Examination and Laboratory Findings

Patients with pancreatic cancer usually have an unremarkable physical examination, but the most common abnormal physical finding is jaundice, which may be accompanied by cutaneous excoriations related to pruritus.

In patients with advanced disease, temporal muscle wasting, hepatomegaly or a nodular liver, left supraclavicular adenopathy (Virchow's node), periumbilical adenopathy (Sister Mary Joseph's nodes), or the unusual finding of a drop metastasis at Blumer's shelf may be discovered on digital rectal examination. Laboratory studies often reveal mild to moderate hyperglycemia and abnormal liver enzymes but not necessarily hyperbilirubinemia. Hyperamylasemia and hyperlipasemia are uncommon in patients with ductal adenocarcinoma but may be seen in patients with IPMN. A normochromic anemia or mild hypoalbuminemia may reflect the chronic nature of the neoplastic process and its nutritional sequelae.

Coagulation tests, particularly a prolonged prothrombin time, may be seen in deeply jaundiced patients due to malabsorption of fat-soluble vitamins.

Diagnostic Imaging

In recent history, pancreatic lesions were evaluated with a combined treatment and diagnostic phase. Patients evaluated with this approach were surgically explored, and through palpation their tumors were deemed resectable or unresectable. In patients with resectable disease, tumor extirpation was then completed during the same procedure, while patients found to have unresectable tumors were treated with operative biliary and gastric bypass. This approach should be abandoned. A separate diagnostic evaluation should precede operative resection of the tumor. The advantages to this approach are: (1) exploration can be limited to those patients with a high likelihood of resection, (2) objective criteria can be utilized to assess resectability rather than subjective imprecise tactile perception, (3) patients who will require venous reconstruction at time of resection can be identified, optimizing preoperative planning, (4) patients may move on to neoadjuvant therapy appropriate for their stage of tumor without an initial exploration, and (5) patients exhibiting an advanced tumor can be palliated with less morbid nonoperative procedures.

Multiphase Multidetector Helical Computerized Axial Tomography

Among diagnostic imaging techniques, abdominal CT scanning is the most common for confirming suspected pancreatic malignancy. Standard CT techniques are relatively insensitive for the assessment of resectability. However, vascular involvement and liver metastases can be most optimally assessed with newer CT imaging techniques. The cornerstone of diagnostic evaluation of a pancreatic tumor is the multiphase CT scan, coordinating intravenous contrast administration with subsequent rapid thin cut CT through the pancreas during arterial, portal venous, and parenchymal phases of enhancement. This must be obtained on a multidetector row helical CT scanner, allowing acquisition during a single breathhold for each phase. With this type of CT, extension of the tumor to the superior mesenteric artery (SMA) , celiac axis, SMV-PV complex, and contiguous structures can be clearly determined, as well as an assessment of distant metastasis.

Optimally, CT imaging should precede stent placement and biopsy due to the possibility of postprocedure inflammation from the biopsy and artifact from the stent, which can confound interpretation of the images.

Resectability is defined on multiphase CT by (1) the absence of metastases outside the pancreas and the pancreatic nodal basin, (2) patency of the SMV-PV, and (3) presence of a definable fat plane between the SMA, celiac artery, and pancreatic mass. Some centers also include SMV-PV invasion as a criteria for unresectability, while others approach vein invasion with segmental resection of the SMV-PV and reconstruction (discussed below).

Absence of a fat plane between the pancreatic mass and the right lateral margin of the SMV-PV identifies tumor invasion of the vein or fibrosis and defines the patient who may require a vein reconstruction at the time of resection. Reports confirm the predictive power of preoperative multiphase CT scan in establishing resectability of pancreatic adenocarcinoma.

Some investigators recommend the use of curved planar reformations and CT angiography in addition to multiphase CT scanning to enhance detection of vessel invasion. Helical CT is poor at predicting nodal involvement, and its accuracy is decreased following neoadjuvant therapy.

Magnetic Resonance Imaging

To date, MRI has not been widely used to assess pancreatic cancer. This method was initially limited by long scanning times and the resultant artifact caused by organ motion. Dynamic MRI, with rapid scanning sequences and bolus intravenous contrast enhancement, however, is reported to have sensitivity and specificity comparable to those for helical CT. Some investigators have found MRI more accurate at predicting malignancy of the pancreatic duct due to findings of concurrent magnetic resonance cholangiopancreatography, but use of this imaging method for pancreatic cancer is currently not widespread.

Ultrasonography

Other investigators have found preoperative ultrasonography useful in assessing tumor characteristics and resectability of pancreatic adenocarcinoma. Calculli et al. report that in 95 patients sonography had high sensitivity and specificity (92.3% and 72.7%, respectively) in defining SMV-PV invasion, although lower than helical CT (98% and 79%, respectively). Minniti et al. found sonography to be superior to CT in identifying the primary tumor (95.3% vs. 89.1%, respectively) but less accurate i n predicting resectability (81.4% vs. 86%, respectively) i n blinded studies o f 64 patients. In contrast, Morrin et aJ. studied 23 patients with periampullary cancer using both multiphase helical CT and ultrasonography with Doppler and found close congruence both in the ability of the two studies to predict vascular involvement and in the poor ability to image metastases. Ultrasonography and CT were in agreement in all cases of unresectable disease. Ultrasonography in pancreatic cancer, as in other diseases, is particularly operator dependent, and in experienced hands may safely replace assessment with helical CT.

Endoscopic Ultrasonography

EUS can image the primary cancer and be a means of obtaining a FNA of pancreatic adenocarcinoma, but in general the procedure is noncontributory when CT scan characterizes the tumor. When a mass cannot be visualized on CT scan, sonography through the wall of the stomach or duodenum can image tumors in the body or tail and head of the pancreas, respectively.

Tissue diagnosis is not necessary prior to routine resection. A suspicious lesion by imaging should be treated with resection. But in specific patients a tissue diagnosis may be needed, such as in patients entering a clinical trial, prior to neoadj uvant therapy, and prior to chemotherapy in advanced tumors. In these patients, an EUS can be highly accurate. Raut et al. found this evaluation has a sensitivity for histologic diagnosis of 91% with a specificity of 100% in testing 216 patients with a pancreatic mass. Like standard ultrasonography, this method is highly operator dependent, and only experienced groups can expect this level of accuracy.

Endoscopic Retrograde Cholangiopancreatography

ERCP delineates pancreatic duct and common bile duct anatomy from brushings and ductal lavage and is a means of obtaining cytologic diagnosis. But, similar to EUS, in the face of a defining CT scan, its findings are often redundant. Pancreatitis, bleeding, and perforation are severe complications associated with ERCP and preclude the routine use of this modality in all pancreatic cancer patients.

ERCP should be reserved for patients in need of endoscopic stenting, equivocal findings on standard evaluation, or for patients in whom tissue diagnosis is needed, such as those in a clinical study, with advanced disease, or anticipating neoadj uvant therapy. Unfortunately, brushings during ERCP have a relatively low yield. Farnell et al. note that surgery may be delayed and rendered more difficult due to the complications that can accompany preoperative ERCP.

If neoadj uvant therapy is being considered, endoscopy of the upper gastrointestinal tract is the most valuable initial step in the management of patients who present with obstructive jaundice from presumed carcinoma of the pancreas. During this procedure, biliary outflow can be reestablished with the placement of an endobiliary stent, and EUS-FNA can be performed.

Some centers prefer percutaneous CT-FNA; however, CT-FNA is operator dependent and is not possible if the lesion is not visible on CT. Although CT-FNA is generally safe, serious complications such as hemorrhage, pancreatitis, fistula, abscess, and death have been reported. Additionally, there have been reports of tumor seeding along the subcutaneous tract of the needle and concerns regarding tumor dissemination by the act of capsular disruption of the neoplasm.

Staging Laparoscopy

Laparoscopy and multi phase CT have evolved concurrently as methods to evaluate a pancreatic mass . Both have emerged as highly effective in evaluating the tumors, but CT as a noninvasive modality supplants the use of routine laparoscopy. Laparoscopy that precedes planned resection can accurately identify metastases that avoid detection by CT, and when combined with laparoscopic ultrasound, can delineate vascular invasion as well as metastases within the hepatic parenchyma.

Minnard et al. found that 90 patients studied who had laparoscopy with sonography had accurate determination of resectability, and Pietrabissa et al. found in 50 patients that laparoscopy with sonography identified hepatic metastases not seen by CT in 8% of patients.

Currently, routine use of laparoscopy is not warranted. Few patients will have findings on laparoscopy that add to information found at CT scanning. The group at JHMI retrospectively reviewed 188 cases of patients studied preoperatively using CT and treated through a laparotomy. Preoperative laparoscopy would have benefited a maximum of 2.3% of patients with a pancreatic head tumor. Lesions in the body and tail were more likely to have misleading CT scans (35.3%). A consensus panel convened by the American Hepato-Pancreato-biliary Association recommends laparoscopy be limited to select patients with primary tumors greater than 3 em in diameter, body or tail tumors, equivocal findings of metastasis on CT, and CA 19-9 level greater than 100 U/mL. Using these criteria, the subset of patients with advanced tumors not identified on CT scan can be accurately assessed by laparoscopy, and patients likely to not have additional findings can be spared the expensive, time-consuming procedure.

5.12. TNM-CLASSIFICATION

T – Primary Tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ*
T1 Tumour limited to pancreas, 2 cm or less in greatest dimension
T2 Tumour limited to pancreas, more than 2 cm in greatest dimension
T3 Tumour extends beyond pancreas, but without involvement of coeliac axis or superior mesenteric artery
T4 Tumour involves coeliac axis or superior mesenteric artery

Note: **Tis also includes the 'PanIN–III' classification.*

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M – Distant Metastasis

M0 No distant metastasis
M1 Distant metastasis

Stage grouping			
Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

5.13. TREATMENT

Operative Treatment

Rationale for Resection

Resectable pancreatic cancers are confined to the pancreas and draining lymph nodes with a patent SMV-PV and noninvolvement of the visceral arteries. Operative excision remains the standard of care in the United States, although justification for resection is based on few obj ective data. There has not been a randomized trial studying subjects with resectable tumors who are randomized to operative versus nonoperative treatment (just as there are no randomized trials for resection of any other type of primary gastrointestinal tumor). Without these trials, the impact of surgical removal is based on comparisons of disparate patient groups and small, single-institution experiences.

It is therefore difficult to evaluate the oncologic aims for operative treatment, including cure of pancreatic cancer and prolongation of survival. Although resection offers the only prospect of long-term survival or cure in this disease, it rarely accomplishes either of these. Conlon et al. analyzed 357 patients with pancreatic cancer who were resected with curative intent from 1981 to 2001 at the Mayo Clinic. An 18% 5-year survival was observed with survival of 62 patients. Ten of these patients subsequently died of metastatic pancreatic cancer beyond the 5 -year time point.

Yeo et al. at JHMI reviewed pancreatic head resections for pancreatic cancer showing 22 of 149 patients undergoing resection were alive at 5 years, noting most deaths later than 5 years were due to metastatic disease. Additionally, Cleary et al. found 18 of 123 patients who were resected during the time period 1988 to 1996 were 5-year survivors. Four of these 18 patients died of metastatic disease after the 5-year time point. All of these studies reveal the 5-year survival of patients treated with pancreatic cancer resection is low.

Many of the patients who surpass the 5-year survival target eventually die of the disease, and cure is realized in a very small number of patients who undergo resection.

If operative treatment rarely cures pancreatic cancer, resection can also be justified as a means to prolong survival; but there is a paucity of studies addressing whether removal of a primary pancreatic cancer prolongs life. Review of the National Cancer Data Base identified 9,559 patients with stage I pancreatic cancer. Of these 6,380 were likely eligible for resection based on age, comorbidities, or acceptance of surgery. Of these candidates for surgery, 2,736 were actually treated with pancreatectomy.

Median survival in those patients with stage I disease treated with surgery was 10.9 months longer than those seemingly eligible patients who did not undergo surgery (19.3 months vs. 8.4 months). Similarly, 5-year survival rates were higher in the operative patients (24.6 vs. 2.9%).

Operative Resection

Operative removal of a pancreatic cancer requires anatomic resections such as pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy that includes contiguous structures (such as the duodenum, spleen, and common bile duct) and at least draining lymph nodes.

The first description of pancreatic head resection with a portion of duodenum was by Codvilla in 1898. This Italian surgeon, who is most known for advances in orthopedic surgery, operated on a j aundiced patient allegedly diagnosed with pancreatic cancer. In this case survival was limited to 24 days following the procedure. Kausch85 described the first successful resection of the pancreatic head with a portion of the duodenum performed in 1909. Whipple embarked on perfecting pancreas head resection in 1934, and in the subsequent 30 years he and contemporary surgeons of the period revised the resection to a technique resembling that used by most surgeons today. Early historical procedures utilized a two-stage approach with an initial biliary bypass. Patients demonstrated hepatic dysfunction due to biliary obstruction, and the initial drainage procedure allowed for normalization of coagulopathy prior to a second procedure during which varying amounts of the pancreatic head and duodenum were resected. An evolving understanding of the coagulopathy and the addition of vitamin K to the preoperative regimen of these patients allowed for single-stage procedures to be routinely completed in the 1940s.

The first description of a distal pancreatectomy was by Trendelenburg in 1882, allegedly for sarcoma involving the spleen and tail of pancreas. The patient did not survive the procedure. In 1889, Ruggi and Briggs separately completed succes sful distal pancreatectomies for alleged malignant lesions, with patient survival at short-term follow-up. Evans et al. has described a stepwise methodology that can be applied to pancreaticoduodenectomy and is widely applicable to most resections. This can be summarized as six steps of resection followed by four steps of reconstruction.

An essential component to this resection is the approach to the SMA margin. This margin extends along the interface of the uncinate process and the length of the SMA, incorporating autonomic nerves at this interface. An RO resection is defined by the absence of microscopic disease at this margin and is correlated with prolonged survival. Although the extent of disease in some tumors precludes an RO resection, a complete resection should be sought when at all feasible.

Intraperitoneal Drains

Intraperitoneal drains are usually placed intraoperatively in the vicinity of the pancreatic and biliary anastomosis following pancreas resection. A single study prospectively evaluated the contribution of this drainage to the postoperative course.

One hundred seventy-nine patients who underwent pancreatic resection (pancreaticoduodenectomy: 139, distal pancreatectomy: 40) were randomized to have drains (88 patients) or no drains (91 patients) placed at the conclusion of the case.

Placement of drains did not decrease the need for subsequent percutaneous drainage of an intra-abdominal collection (drain: eight patients, no drain: seven patients) and the incidence of intraperitoneal sepsis, fluid collection, or fistula was increased in the patients who were randomized to intraperitoneal drain (drain: 19 patients, no drain: eight patients). Accordingly, the use of intraperitoneal drains is decreasing among pancreatic surgeons.

Biliary Stents

Seventy percent of resectable pancreatic cancers obstruct the distal common bile duct (CBD) at presentation. The intrapancreatic portion of the CBD passes behind or through the pancreatic head, rendering it susceptible to mass effect and obstruction from the tumor or associated desmoplasia. In many patients, hyperbilirubinemia precipitates the diagnosis of a mass in the pancreatic head.

Biliary stents relieve obstruction and are inserted using percutaneous transhepatic or endoscopic techniques, and their use in patients with resectable lesions can maintain a patent CBD during neoadjuvant therapy or referral to a regional center with a focus on pancreatic cancer. Soft silastic stents can be changed periodically and are most commonly used, but they can fail during a prolonged period of neoadj uvant therapy. Expandable metal stents do not have the interchangeability of silastic stents but are more durable. When placed in patients with resectable tumors, the most superior extent of the stent should be at the confluence of the cystic duct and the common bile duct, allowing division of the common bile duct above the cystic duct entrance in any subsequent procedure. A metal stent cannot be divided intraoperatively. Therefore, a metal stent cannot traverse a planned line of common bile duct division.

The morbidity associated with biliary stents has recently come into focus, raising questions regarding their safety in patients with resectable pancreatic head lesions. Povoski et al. at

MSKCC analyzed the clinical course of 240 patients treated by pancreaticoduodenectomy, 131 for pancreas adenocarcinoma. Overall, 175 patients were evaluated with biliary instrumentation, primarily ERCP, and 126 patients were treated with one or more drainage procedures using a stent (70.5 % endoscopic and 19.9% percutaneous) or operative procedure (9.6%). Forty-eight percent of patients developed a postoperative complication, and biliary drainage by stent or operation was associated with an increased complication risk compared to those patients not treated with drainage (55% vs. 39% respectively; P = .025). Specifically, risk of infectious complication (41% vs. 25% ; P =.014), intra-abdominal abscess (24% vs. 9% ; P = .020), and death (8% vs. 3% ; P = .037) were all increased with biliary drainage.

Several retrospective studies have recently challenged these findings, associating fewer complications with the use of preoperative stents. These groups found no stemrelated morbidity or an association between stents and wound infection or wound infection and pancreatic fistula during the postoperative period for pancreaticoduodenectomy. One of these investigators, Pisters et al. at M. D. Anderson Cancer Center (MDACC) comprehensively scrutinized 300 consecutive patients treated with pancreaticoduodenectomy, finding 172 had been decompressed with a prosthetic stent, 35 with operative bypass, and 93 not drained. Only wound infection was found to be associated with preoperative biliary stenting (stent 13% vs. no stent 4%; P = .029). The bacterial species identified by intraoperative bile culture and at any subsequent wound infection are frequently the same, so the results of an intraoperative bile culture can direct antimicrobial choice when a wound infection is initially suspected.

Preoperative endobiliary stenting is a safe intervention that results in increased rates of postoperative wound infection, but should not be avoided when used to palliate patients for transfer to a high-volume center. Birkmeyer et al,97,98 clearly establish that transfer of patients with pancreatic cancer to high-volume centers significantly decreases patient morbidity and mortality. Inasmuch as endobiliary stenting can facilitate this transfer, the maneuver should not be abandoned. Stenting additionally can temporize biliary obstruction for the completion of neoadjuvant therapy.

Adjuvant and Neoadjuvant Therapy

Adjuvant therapy, as properly defined, involves the delivery of anticancer therapy after surgical removal of all gross tumor to prevent tumor recurrence. Despite documented reductions in mortality related to surgery, improvements in radiation, and more active chemotherapy, little survival benefit has been demonstrated for adj uvant therapy in pancreatic cancer.

Adjuvant Studies Using 5 -Fluorouracil-Based Chemoradiation

Since resected pancreatic cancer has a propensity to recur locally, early studies of adjuvant therapy focused on radiation to prevent local relapse with delivery of systemic therapy to inhibit distant failure. There have been several randomized and nonrandomized trials of adj uvant 5-fluoroucil (5-FU)-based chemoradiotherapy. The three randomized trials that have received the most attention were conducted by the Gastrointestinal Study Group (GITSG), the European Organisation for Research and Treatment of Cancer (EORTC) , and the European Study Group for Pancreatic Cancer (ESPAC) JOS-107.

The first was the GITSG trial, which enrolled patients with completely resected pancreatic cancer and, importantly, microscopically negative margins (RO). Forty-six patients were randomized to undergo observation or bolus 5-FU (500 mg/m2 daily) during the first 3 days of each period of split course radiation (20 Gy in 10 fractions, 2 weeks break, and resumption of radiation to a total dose of 40 Gy) , followed by up to 2 years of weekly bolus 5-FU. Survival was reported after only 43 patients had completed treatment and showed a striking survival advantage for patients receiving combined modality therapy compared with surgery alone (median 21.0 months vs. 10.9 months, respectively; one-tailed P = .03).

The GITSG findings could not b e reproduced by a subsequent EORTC trial. EORTC-40891 randomized 218 patients preoperatively for resection of tumors of the periampullary region (including pancreatic head, common bile duct, papilla of Vater, and duodenal cancers), to either undergo observation or receive 5-FU (25 mg/kg/d to a maximum dose of 1,500 mg/d) given concurrently during the first week of two split courses of radiation (total dose 40 Gy) . Subgroup analysis for the 114 patients with cancer of the pancreatic head showed a trend toward improved overall survival for those receiving adjuvant therapy versus the observation group (median 17.1 months vs. 12.6 months, respectively) , but the difference was not statistically significant (P = .099) . Updated data from this trial were published in 2008 and again showed no survival advantage for the patients randomized to chemoradiation. At about the same time, ESPAC launched an ambitious trial to determine the efficacy of chemotherapy versus chemoradiation on overall survival after surgery. ESPAC-1 enrolled 289 patients from 53 European hospitals. After resection, patients were randomized to one of four arms: observation, chemotherapy with bolus 5-FU (425 mg/m2) and leucovorin (20 mg/m2) daily for 5 days every 28 days for 6 months, chemoradiation with bolus 5-FU 500 mg/m2 during the first 3 days of splitcourse of radiation (as in the GITSG trial), or chemoradiation followed by 6 months of chemotherapy with bolus 5-FU and leucovorin. When overall survival of the four arms were directly compared, there was no statistically significant difference in survival.

However, the study was designed to analyze survival outcomes using a two-by-two factorial design according to treatment assignment to chemotherapy (yes or no) or to chemoradiation (yes or no).

Patients who received chemoradiation did worse (median survival of 1 5.9 months; hazard ratio [HR] for death 1.28; 95% CI, 0.99 to 1. 66) than those who did not receive chemoradiation (median survival of 17.9 months; P=.05). Conversely, patients who received chemotherapy had a median survival of 20.6 months (HR for death 0.71; 95% CI, 0.55 to 0.92) versus 15.5 months for those patients who did not receive chemotherapy, a statistically significant improvement (P = .009). The investigators concluded that chemoradiation not only failed to benefit patients but also reduced survival when given before chemotherapy.

The merits of chemoradiation have been increasingly challenged over time, and the role of radiation as a component of adjuvant therapy should be considered an open question, with two current adj uvant trials trying to determine if there is a benefit. The EORTC is conducting a randomized trial comparing systemic gemcitabine therapy alone versus systemic gemcitabine followed by gemcitabine-based chemoradiation. The Radiation Therapy Oncology Group (RTOG) is delivering five cycles of gemcitabine with or without erlotinib as part of the first randomization. Thereafter, all patients will be restaged and for those without interval development of metastatic disease, a sixth cycle of gemcitabine will be delivered (with or without erlotinib) and a second randomization will occur to assign patients to no further therapy or to a standard course of 5-FU based chemoradiation.

Radiation Technique: Postoperative Adjuvant Radiation Therapy

Postoperative radiation therapy has evolved from the early trials, and patients with resected disease are typically treated with 50.4 Gy, given in 1.8 -Gy fractions. Field reductions are characteristic after 45 Gy. The boost volume should include the superior mesenteric vessels, the tumor bed, and the celiac axis. A four-field technique using anterior, posterior, and opposed lateral fields allows sparing of critical tissues. Fields are weighted so that the dose contribution from the lateral fields is restricted to 20 Gy by weighting the anteroposterior-posteroanterior fields at twice that of the lateral fields. This approach prevents the liver and kidney tissue that are restricted to the lateral fields from receiving doses beyond their tolerance. In cases where the right kidney is receiving a toxic dose, the posterior field may be omitted or customized oblique fields used. Intensity modulated radiation therapy (IMRT) is not likely to result in a reduction of toxicity, but should be considered in cases where there are grossly enlarged lymph nodes or a positive margin. In these cases, a nested gross tumor volume can be used to deliver a higher dose. A simultaneous dose of 63 Gy in 2 8 fractions can be delivered to high-risk areas and 50.4 Gy to the microscopic areas at risk, avoiding the jejunal reconstruction. Although this practice is standard, there are no studies that demonstrate that higher doses of radiation compensate for a positive margin.

The celiac axis, which is most commonly located at T12, should be covered with a 2-cm margin superiorly. That superior border usually covers the porta hepatis as well. Inferiorly the tumor and duodenal bed should be covered with a 2-cm margin. The left border is usually placed 2 em to the left of the vertebral body edge, as long as coverage of the preoperative tumor volume is adequate. The preoperative tumor volume and preoperative location of the duodenum define the right field border and the anterior extent of the lateral fields. The porta hepatis identified on the planning CT scans should be covered, and useful landmarks for the porta hepatis are the bifurcation of the portal vein and the hepatic artery. For lesions of the pancreatic body and tail, similar fields are used except that the splenic hilum is covered and the porta hepatis and duodenal bed are not covered. The right field border is typically located 2 cm from the right vertebral body edge.

Gemcitabine or 5 -FU as Adjuvant Therapy

Given the modest superiority of gemcitabine over 5-FU for the treatment of patients with advanced disease, these two drugs have been compared head to head in the adj uvant setting. The RTOG performed a prospective randomized trial (RTOG 9704) comparing systemic gemcitabine with infusional 5-FU; patients in both arms also received 5-FU-based chemoradiation.

A total of 518 patients were enrolled in the study, with the maj ority of patients having tumors of the pancreatic head. There was no survival difference between patients randomized to gemcitabine and those who received infusional 5-FU. However, among the 380 patients with resected head lesions, survival was seemingly superior for patients randomized to gemcitabine compared with those who received infusional 5-FU (20.5 months vs. 16.9 months; HR for death 0.82; 95% CI, 0.65 to 1.03; P = . 09).

The most recent results comparing systemic gemcitabine to systemic 5 -FU come from the largest adj uvant phase 3 trial ever conducted, ESPAC-3. The results have not as yet been published, but they were presented at the 2009 ASCO Annual Meeting. The original trial design randomized patients to one of three arms: observation, bolus 5-FU and leucovorin, or gemcitabine. A total of 1088 patients were randomized to receive either five daily doses of 5 -FU (425 mg/m2 IV bolus) with leucovorin (20 mg/m^2 IV bolus) every 28 days for six cycles or gemcitabine (1,000 mg/m2 weekly for 3 of 4 weeks). With a median follow-up o f 34 months, there was no difference between the treatment arms . Median survival was 23.0 months in the 5-FU arm and 23.6 months in the gemcitabine arm (P =0.39). As in ESPAC-1 , these results lent credence to 5-FU and leucovorin as effective adj uvant chemotherapy. However, toxicity associated with gemcitabine was less than that observed using 5-FU and leucovorin. Taken together, the results from the RTOG trial and ESPAC-3 (v2) suggest that gemcitabine is either slightly better than 5-FU in terms of efficacy or slightly better tolerated, and at present, gemcitabine monotherapy has emerged as the standard of care for adjuvant therapy.

5.13. QUESTIONS FOR SELF-CONTROL

1. Describe incidence, major causes, growth patterns and clinical symptoms of hepatocellular carcinoma.
2. Name the types of diagnostic methods used in liver tumour detection.
3. Describe methods of treatment used in liver malignancies.
4. What are the causes of pancreatic cancer?
5. What are the clinical symptoms of pancreatic cancer?
6. Which diagnostic algorithm is generally used for pancreatic cancer?
7. Name the types of operations used in cases of pancreatic cancer.

5.14. TESTS FOR SELF-CONTROL

1. The most common primary malignant hepatic tumour is:
    a. Basal cell carcinoma
    b. Squamous cell carcinoma
    c. Cholangiocellular carcinoma
    d. Hepatocellular carcinoma
2. Globally, the common causes of hepatocellular carcinoma are:
    a. HBV and HCV
    b. Aflatoxins and alcohol
    c. Cirrhosis
    d. All of the above
3. Clinical presentation of carcinoma of the head of pancreas is:
    a. Constipation
    b. Dysphagia and odynophagia
    c. Painless obstructive jaundice
    d. bleeding
4. 80% of all pancreatic cancers account histologically for:
    a. Adeno-squamous carcinoma
    b. Papillary cystic carcinoma
    c. Adenocarcinoma
    d. Giant cell carcinoma
5. Tumour marker for pancreatic cancers is:
    a. CA 125
    b. PSA
    c. CA 19-9
    d. AFP

Correct answers: 1d, 2d, 3c, 4c, 5c

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