MINISTRY OF HEALTH OF UKRAINE
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY

METHODICAL RECOMMENDATIONS

FOR PREPARING TO PRACTICAL CLASSES
FROM DISCIPLINE "ONCOLOGY"

PART II

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 6
COLORECTAL CANCER

CANCER OF THE COLON

6.1. EPIDEMIOLOGY

Globally, nearly 1 ,200,000 new colorectal cancer cases are believed to occur, which accounts for approximately 10 % of all incident cancers, and mortality from colorectal cancer is estimated at nearly 609,000. In 2010 there were an estimated 141,570 new cases of colorectal cancer and 51,370 deaths in the United States. As such, colorectal cancer accounts for nearly 10% of cancer mortality in the United States. Prevalence estimates reveal that in unscreened individuals age 50 years or older, there is a 0.5% to 2.0% chance of harboring an invasive colorectal cancer, a 1.0% to 1.6% chance of an in situ carcinoma, a 7% to 10% chance of a large (1 cm or larger) adenoma, and a 25% to 40% chance of an adenoma of any size.

Age impacts colorectal cancer incidence greater than any other demographic factor. To that end, sporadic colorectal cancer increases dramatically above the age of 45 to 50 years for all groups. In almost all countries, age-standardized incidence rates are less for women than for men. Although colorectal cancer incidence has been steadily decreasing in the United States and Canada, the incidence is rapidly increasing in Japan, Korea, and China. In the United States from 2002 to 2006, the age-standardized incidence rates per 100,000 population was 59.0 for men and 43.6 for women when combined for all races. Recognizing that decreases in age-standardized colorectal cancer incidence and mortality rates are apparent in the United States over the past 10 to 15 years, such trends may be counterbalanced by prolonged longevity.

6.2. ETIOLOGY, RISK FACTORS

<u>Inherited Predisposition</u>

Family history confers an increased lifetime risk of colorectal cancer, but that enhanced risk varies depending on the nature of the family history. Familial factors contribute importantly to the risk of sporadic colorectal cancer, depending upon the involvement of first- or second-degree relatives and the age of onset of colorectal cancer. Involvement of at least one first-degree relative with colorectal cancer serves to double the risk of colorectal cancer.

There is further enhancement of the risk if a case is affected prior to the age of 60. Similarly, the likelihood of harboring premalignant adenomas or colorectal cancer is increased in first-degree relatives of persons with colorectal cancer. The National Polyp Study reveals compelling data; the relative risk for parents and siblings of patients with adenomas compared to spousal controls was 1.8, which increased to 2.6 if the proband was younger than age 60 at adenoma detection.

Provocative assessments of population groups suggest a dominantly inherited susceptibility to colorectal adenomas and cancer, which may account for the majority of sporadic colorectal cancer, but this may have variable inheritance based on the degree of exposure to environmental factors. What are these susceptibility factors? The answer has yet to emerge. Nonetheless, genetic polymorphisms may be of paramount importance, such as in glutathione-s-transferase, ethylene tetrahydrofolate reductase and N-acetyltransferases, especially NAT1 and NAT2. In fact, genetic polymorphisms can vary among different racial and ethnic groups, which may provide clues to the geographic variation of colorectal cancer as well.

Environmental Factors

Seminal studies have underscored the importance of environmental factors as contributing to the pathogenesis of colorectal cancer.

One has to take population-based studies into the context of methodologies employed, lead-time bias, time-lag issues, definition of surrogate and true end points, and the role of susceptibility factors.

Diet
Total Calories

Obesity and total caloric intake are independent risk factors for colorectal cancer as revealed by cohort and case-control studies. Increased body mass may result in a twofold increase in colorectal cancer risk, with a strong association in men with colon but not rectal cancer.

Meat, Fat, and Protein

Ingestion of red meat but not white meat is associated with an increased colorectal cancer risk, and as such, per capita consumption of red meat is a potent independent risk factor. Whether the total abstinence from red meat leads to a decreased colorectal cancer incidence has not been clarified, as there are studies with opposing resultsY Fried, barbecued, and processed meats are also associated with colorectal cancer risk, especially for rectal cancer, with odds ratio of 6.38. Although high protein intake may augment carcinogenesis, definitive proof of this is lacking. Mechanistically, a high protein diet is associated with accelerated epithelial proliferation.

Fatty components of red meat may be tumor promoters, as fats may be metabolized by luminal bacteria to carcinogens, which would cause abnormal colonic epithelial proliferation. There is controversy as to whether the type of fat is important. Some studies suggest that saturated animal fats may confer especially high risk, and yet other investigations suggest that there is no evidence for increased risk for any specific dietary fat after adj ustment for total energy intake.

Fiber

Classically, a high fiber diet was associated with a low incidence of colorectal cancer in Africa, with numerous studies substantiating this premise. Protection was believed to be afforded from wheat bran, fruit, and vegetables. A high-fiber diet was believed to dilute fecal carcinogens, decrease colon transit time, and generate a favorable luminal environment. However, these canonical concepts have been challenged by more recent, large, well-controlled studies that showed no inverse relationship between colorectal cancer and fiber intake. In a study of nearly 90,000 women from ages 34 to 59 who were followed for 16 years, no protective effect was noted between fiber and incidence of either adenomatous polyp or colorectal cancer. This was further corroborated by two large randomized controlled trials that evaluated high-fiber diets for moderate duration and discovered a lack of effect on the number, size, and histology of polyps found on colonoscopy. At this point, therefore, the majority of evidence suggests that dietary fiber does not play a role in the risk of developing colorectal cancer.

Vegetables and Fruit

A protective effect of vegetables and fruits against colorectal cancer is generally believed to be true. This has been observed with raw, green, and cruciferous vegetables. Whether certain agents such as antioxidant vitamins (E, C, and A), folate, thioethers, terpenes, and plant phenols may translate into effective chemopreventive strategies requires further investigation, although the data for folate intake are sound.

Calcium also has been historically implicated as having a protective effect. Mechanistically, calcium can be viewed as being able to bind inj urious bile acids with reduction of colonic epithelial proliferationY This is supported through cell culture models.

Lifestyle

Physical inactivity has been associated with colorectal cancer risk, for colon more than rectal cancer. A sedentary lifestyle may account for an increased colorectal cancer risk, although the mechanism is unclear. More recent data suggest that physical activity after the diagnosis of stages I to III colon cancer may reduce the risk of cancer-related and overall mortality, and that the amount of aerobic exercise correlates with a reduced risk of recurrence following resection of stage III colon cancer. Most studies of alcohol have demonstrated at most a minimally positive effect. Associations are strongest between alcohol consumption in men and risk of rectal cancer. Perhaps interference with folate metabolism through acetaldehyde is responsible.

Prolonged cigarette smoking is associated with the risk of colorectal cancer. Cigarette smoking for greater than 20 pack-years was associated with large adenoma risk and greater than 35 pack-years with cancer risk. There has been no reproducible association in the chronic use of either coffee or tea with colorectal cancer risk.

Drugs
Nonsteroidal Anti-Inflammatory Drugs

Population-based studies strongly support inverse associations between use of aspirin and other nonsteroidal anti-inflammatories (NSAIDs) and the incidences of both colorectal cancer and adenomas. In a cohort study the relative risk of colorectal cancer was 0.49 (95% confidence interval [CI] , 0.24 to 1.00) when comparing regular NSAID users with nonusers. Duration of NSAID use is important, and right-sided colon cancers may benefit more than left-sided colorectal cancers. Interestingly, the type of NSAID was not important. As a result of this and other studies, NSAIDs and selective cyclooxygenase 2 (COX-2) inhibitors have been investigated intensively in familial adenomatous polyposis (FAP) and sporadic colorectal cancer.

6.3. DIAGNOSIS

Symptoms associated with colorectal cancer include lower gastrointestinal bleeding, change in bowel habits, abdominal pain, weight loss, change in appetite, and weakness, and in particular, obstructive symptoms are alarming. However, apart from obstructive symptoms, other symptoms do not necessarily correlate with stage of disease or portend a particular diagnosis.

Physical examination may reveal a palpable mass, bright blood per rectum (usually left-sided colon cancers or rectal cancer) or melena (right-sided colon cancers), or lesser degrees of bleeding (Hemoccult positive stool) . Adenopathy, hepatomegaly, j aundice, or even pulmonary signs may be present with metastatic disease. Obstruction by colon cancer is usually in the sigmoid or left colon, with resulting abdominal distention and constipation; whereas right-sided colon cancers may be more insidious in nature. Complications of colorectal cancer include acute GI bleeding, acute obstruction, perforation, and metastasis with impairment of distant organ function.

Laboratory values may reflect iron-deficiency anemia, electrolyte derangements, and liver function abnormalities. The carcinoembryonic antigen (CEA) may be elevated and is most helpful to monitor postoperatively, if reduced to normal as a result of surgery.

Evaluation should include complete history, family history, physical examination, and laboratory tests, colonoscopy, and pan-body computed tomography (CT) scan.

Upon completion of the diagnosis and staging (endoscopic ultrasound should be integrated for staging of rectal cancer) , incorporation of expertise from medical, radiation, and surgical oncologists is required to formulate and implement a treatment plan. With the advent of molecular biological techniques, attention has been drawn to stool-based tools and new blood-based tests. Technology now exists to extract genomic DNA or protein from stool and assay for evidence of genetic alterations.

Large-scale validation studies are in progress. One particularly attractive pathway for stool-based diagnostics would be able to stratify patients as high, moderate, or low risk for colorectal cancer and thus influence screening modalities and frequency of screening. In a complementary fashion, functional genomics are being applied to pair-wise comparisons of normal colon and colorectal cancers to sample the entire human genome of nearly 30,000 genes to discover those genes, known and novel, that may be up-regulated or down-regulated and possibly linked to detection, prognosis, and therapy.

6.4. CLINICAL PRESENTATION
Signs and symptoms

The symptoms and signs of colorectal cancer depend on the location of tumor in the bowel, and whether it has spread elsewhere in the body (metastasis). The classic warning signs include: worsening constipation, blood in the stool, weight loss, fever, loss of appetite, and nausea or vomiting in someone over 50 years old. While rectal bleeding or anemia are high-risk features in those over the age of 50, other commonly described symptoms including weight loss and change in bowel habit are typically only concerning if associated with bleeding.

Inflammatory bowel disease

People with inflammatory bowel disease (ulcerative colitis and Crohn's disease) are at increased risk of colon cancer. The risk is greater the longer a person has had the disease, and the worse the severity of inflammation. In these high risk groups both prevention with aspirin and regular colonoscopies are recommended. People with inflammatory bowel disease account for less than 2% of colon cancer cases yearly. In those with Crohn's disease 2% get colorectal cancer after 10 years, 8% after 20 years, and 18% after 30 years. In those with ulcerative colitis approximately 16% develop either a cancer precursor or cancer of the colon over 30 years.

6.5. TNM-STAGING
T – Primary Tumour
TX   Primary tumour cannot be assessed
T0   No evidence of primary tumour
Tis   Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
T1   Tumour invades submucosa

T2   Tumour invades muscularis propria

T3   Tumour invades subserosa or into nonperitonealized pericolic or perirectal tissues

T4   Tumour directly invades other organs or structures and/or perforates visceral peritoneum

T4a   Tumour perforates visceral peritoneum

T4b   Tumour directly invades other organs or structures[2,3]

Notes: 1. Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

2. Direct invasion in T4b includes invasion of other organs or segments of the colorectum by way of the serosa, as confirmed on microscopic examination, or for tumours in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria.

3. Tumour that is adherent to other organs or structures, macroscopically, is classified cT4b. However, if no tumour is present in the adhesion, microscopically, the classification should be pT1–3, depending on the anatomical depth of wall invasion.

N – Regional Lymph Nodes

NX   Regional lymph nodes cannot be assessed

N0   No regional lymph node metastasis

N1   Metastasis in 1–3 regional lymph nodes

N1a   Metastasis in 1 regional lymph node

N1b   Metastasis in 2–3 regional lymph nodes

N1c   Tumour deposit(s), i.e., satellites*, in the subserosa, or in non-peritonealized pericolic or perirectal soft tissue *without* regional lymph node metastasis

N2   Metastasis in 4 or more regional lymph nodes

N2a   Metastasis in 4–6 regional lymph nodes

N2b   Metastasis in 7 or more regional lymph nodes

*Note: *Tumour deposits (satellites), i.e., macroscopic or microscopic nests or nodules, in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma without histological evidence of residual lymph node in the nodule, may represent discontinuous spread, venous invasion with extravascular spread (V1/2) or a totally replaced lymph node (N1/2). If such deposits are observed with lesions that would otherwise be classified as T1 or T2, then the T classification is not changed, but the nodule(s) is recorded as N1c. If a nodule is considered by the pathologist to be a totally replaced lymph node (generally having a smooth contour), it should be recorded as a positive lymph node and not as a satellite, and each nodule should be counted separately as a lymph node in the final pN determination.*

M – Distant Metastasis

M0   No distant metastasis

M1   Distant metastasis

M1a Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node(s))

M1b Metastasis in more than one organ or the peritoneum

Group staging

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
II	T3	N0	M0
	T4	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1	N1	M0
	T2	N1	M0
	T1	N2a	M0
IIIB	T3	N1	M0
	T4a	N1	M0
	T2	N2a	M0
	T3	N2a	M0
	T1	N2b	M0
	T2	N2b	M0
IIIC	T4a	N2a	M0
	T3	N2b	M0
	T4a	N2b	M0
	T4b	N1	M0
	T4b	N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

6.6. TREATMENT

Management

The treatment of colorectal cancer depends on how advanced it is. When colorectal cancer is caught early surgery can be curative. However, when it is detected at later stages (metastases are present), this is less likely and treatment is often directed more at extending life and keeping people comfortable.

Surgery

For people with localized cancer the preferred treatment is complete surgical removal with the attempt of achieving a cure. This can either be done by an open laparotomy or sometimes laparoscopically. If there are only a few metastases in the liver or lungs they may also be removed. Sometimes chemotherapy is used before surgery to shrink the cancer before attempting to remove it. The two most common sites of recurrence if it occurs is in the liver and lungs.

Chemotherapy

Chemotherapy may be used in addition to surgery in certain cases as adjuvant therapy. If cancer has entered the lymph nodes adding the chemotherapy agentsfluorouracil, or capecitabine increases life expectancy. If the lymph nodes do not contain cancer the benefits of chemotherapy are controversial. If the cancer is widely metastatic or unresectable, treatment is then palliative. Typically in this case a couple of different chemotherapy medications are used. Chemotherapy drugs may include combinations of agents including fluorouracil, capecitabine, UFT, leucovorin, irinotecan, or oxaliplatin.

Radiation

While a combination of radiation and chemotherapy may be useful for rectal cancer, its use in colon cancer is not routine due to the sensitivity of the bowels to radiation.

Palliative care

In people with incurable colorectal cancer, palliative care can be considered for improving quality of life. Surgical options may include non-curative surgical removal of some of the cancer tissue, bypassing part of the intestines, or stent placement. These procedures can be considered to improve symptoms and reduce complications such as bleeding from the tumor, abdominal pain and intestinal obstruction. Non-operative methods of symptomatic treatment include radiation therapy to decrease tumor size as well as pain medications.

Aspirin

A 2012 study reported regular aspirin use in those with mutated-PIK3CA colorectal cancer, but not wild-type PIK3CA cancer, had improved survival rates.

Prognosis

In Europe the five-year survival for colorectal cancer is less than 60%. In the developed world about a third of people who get the disease die from it.
Survival is directly related to detection and the type of cancer involved, but overall is poor for symptomatic cancers, as they are typically quite advanced. Survival rates for early stage detection is about 5 times that of late stage cancers.

For example, patients with a tumor that has not breached the muscularis mucosa (TNM stage Tis, N0, M0) have an average 5-year survival of 100%, while those with an invasive cancer, i.e. T1 (within the submucosal layer) or T2 (within the muscular layer) cancer have an average 5-year survival of approximately 90%. Those with a more invasive tumor, yet without node involvement (T3-4, N0, M0) have an average 5-year survival of approximately 70%.

Patients with positive regional lymph nodes (any T, N1-3, M0) have an average 5-year survival of approximately 40%, while those with distant metastases (any T, any N, M1) have an average 5-year survival of approximately 5%.

According to the American Cancer Society statistics in 2006, over 20% of patients present with metastatic (stage IV) colorectal cancer at the time of diagnosis, and up to 25% of this group will have isolated liver metastasis that is potentially resectable. Lesions which undergo curative resection have demonstrated 5-year survival outcomes now exceeding 50%.

Follow-up

The aims of follow-up are to diagnose, in the earliest possible stage, any metastasis or tumors that develop later, but did not originate from the original cancer (metachronous lesions).

The U.S. National Comprehensive Cancer Network and American Society of Clinical Oncology provide guidelines for the follow-up of colon cancer. A medical history and physical examination are recommended every 3 to 6 months for 2 years, then every 6 months for 5 years. Carcinoembryonic antigen blood level measurements follow the same timing, but are only advised for patients with T2 or greater lesions who are candidates for intervention. A CT-scan of the chest, abdomen and pelvis can be considered annually for the first 3 years for patients who are at high risk of recurrence (for example, patients who had poorly differentiated tumors or venous or lymphatic invasion) and are candidates for curative surgery (with the aim to cure). A colonoscopy can be done after 1 year, except if it could not be done during the initial staging because of an obstructing mass, in which case it should be performed after 3 to 6 months. If a villous polyp, a polyp >1 centimeter or high grade dysplasia is found, it can be repeated after 3 years, then every 5 years. For other abnormalities, the colonoscopy can be repeated after 1 year.

Routine PET or ultrasound scanning, chest X-rays, complete blood count or liver function tests are not recommended. These guidelines are based on recent meta-analyses showing intensive surveillance and close follow-up can reduce the 5-year mortality rate from 37% to 30%.

6.7. QUESTIONS FOR SELF-CONTROL

1. Name the countries with the highest incidence of colorectal cancer.
2. What age is colorectal cancer diagnosed more frequently?
3. What are the causes of development of colon and rectal cancer?
4. What are the main pre-cancerous diseases of the colon and rectum?
5. What parts of colon is affected by cancer more frequently?
6. How does cancer of the colon and rectum spread?
7. How is colorectal cancer diagnosed?
8. How is cancer of colon and rectum treated?

6.8. TESTS FOR SELF-CONTROL

1. Mean age of colorectal cancer incidence is:
   a. 52 years
   b. 72 years
   c. 62 years
   d. 82 years
2. Basic pathogenic reasons of development of colon cancer include all, except:
   a. Action of cancirogenes
   b. Alcohol and Smoking
   c. Proliferations in the intestine
   d. Dysbacteriosis
3. Risk factors of development of colon cancer are:
   a. Lack of vitamin A, E, C
   b. Predisposing diseases
   c. Acromegaly and Barrett`s esophagus
   d. All of the above
4. The first sign of the right colon cancer is:
   a. Anemia
   b. Pathologic discharge
   c. Constipation
   d. Discomfort
5. What is the basic method in diagnostics of colon cancer?
   a. X-ray investigation with Barium enema and colonoscopy
   b. X-ray investigation with Barium (contrast dye) orally
   c. Exploratory laparotomy
   d. Ultrasound

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

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THEME 7
LUNG CANCER

7.1. EPIDEMIOLOGY

Lung cancer is one of the most common malignancies worldwide. During 2009, approximately 219,440 of an estimated 1,449,350 (15%) new cancer cases, and 159,390 of 562,340 (28%) total cancer deaths in the United States were attributable to lung cancer. In the 40 countries comprising Europe, lung cancer accounts for 391,000 (12%) of approximately 3.2 million new cancer cases, and 19.9% (342,000) of cancerrelated deaths.

Lung cancer is rapidly emerging as a maj or cause of mortality in the Middle East, Africa, and Asia as well. Approximately 70,000 annual cancer-related deaths are currently attributed to lung cancer in Japan. More than 130,000 lung cancer deaths occur annually in China; death rates attributable to this disease are expected to increase substantially over the next several decades.

The incidence of lung cancer varies considerably among different ethnic populations throughout the world. Analysis of data from 22 cancer registries in 5 continents revealed that cumulative lung cancer risks were higher in males than females. Among men, African Americans had the highest incidence of lung cancer risk (approximately 7.5%), whereas Swedes had the lowest cumulative risk (approximately 2%). Among women, cumulative lung cancer risk was highest in African Americans (approximately 3.5%), whereas French and Korean women had very low cumulative risks (approximately 1%). More recent data indicate that lung cancer rates for African Americans are converging with that of whites in the United States. Lung cancer risks in East Asian female immigrants within the United States appear comparable to those observed in native populations

7.2. ETIOLOGY, RISK FACTORS

<u>Smoking</u>

Approximately 80% of cases of non-small cell lung cancer (NSCLC) in men and 50% of these neoplasms in women worldwide are directly attributable to cigarette smoking. Age adjusted lung cancer incidence rates range from 174 to 362, and 149 to 293 per 100,000 person-years for male and female active smokers, compared with 45 to 141 and 65 to 179 per 100,000 person-years for male and female former smokers, respectively. In contrast, age-adj usted lung cancer incidence rates range from 4.8 to 13.7 and 14.4 and 20.8 for male and female never-smokers, respectively.

An estimated 1.3 billion people smoke worldwide. In general, the incidence of lung cancer throughout the world reflects the prevalence of cigarette smoking, and evolving patterns of lung cancer appear attributable at least in part to filters, tar content, and other variations in tobacco blends. Whereas tobacco consumption is decreasing in many industrialized nations, cigarette smoking has risen dramatically in developing countries, which lack resources for tobacco control and cancer care.

The effects of cigarette smoke on respiratory epithelial cells are mediated by a complex mixture of organic as well as inorganic carcinogens present in the air/liquid interphase such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) nicotine, benzo(a)pyrene, and cadmium, or vapor phase such as formaldehyde and ethylcarbamate. Cigarette smoke condensate or purified activated tobacco carcinogens such as benzo-(a)-pyrene-diolepoxide-1 induce progressive genetic as well as epigenetic alterations coinciding with malignant transformation in cultured human respiratory epithelia.

Furthermore, purified tobacco carcinogens including NNK and ethylcarbamate induce pulmonary carcinomas in rodents exhibiting histologic and molecular genetic profiles virtually identical to human lung cancers NNK induces expression of type 1 insulin growth factor receptor and activates AKT signaling in respiratory epithelial cells; in addition, NNK activates k-ras, and up-regulates DNA methyltransferase activity in pneumocytes in vitro and in vivo.

Polyaromatic hydrocarbonsin tobacco smoke forms DNA adducts, inducing mutations within tumor suppressor genes such as the p53 , RASSFlA, and FHIT, thereby disrupting cell cycle regulation, DNA repair, and apoptosis. The carcinogenic effects of tobacco smoke are not simply related to NNK and polycyclic aromatic hydrocarbon (PAH) , but are also directly attributable to nicotine as well as inorganic metals such as nickel, arsenic, and chromium. Furthermore, nicotine activates raf-1 kinase, promoting cell-cycle progression in respiratory epithelial cells.

Genetic Predisposition

The fact that only a minority of smokers develop lung cancer suggests a genetic predisposition to this disease. However, to date, the genes conferring susceptibility to this disease have not been fully elucidated. A two- to threefold increased risk of lung cancer has been observed among first-degree relatives of probands with this disease; risk appears most pronounced in individuals with nonsmoking family members who develop lung cancer at an early age, and in families with multiple afflicted members.

An ill-defined gene locus mapping to chromosome 6q confers susceptibility to lung cancer, particularly in never-smokers, and individuals with cumulative tobacco exposures to 20 or less pack-years; additional susceptibility loci map to 1q, 8q, and 9p. Several recent genome-wide association studies have identified major susceptibility loci at 15q25, 5p15, and 6p21. The 15q25 locus contains genes encoding the nicotinic acetylcholinergic receptor subunits CHRNA3 and CHRNA5; interestingly, the association of this locus with lung cancer risk persists after adj usting for smoking.

OccupationaVEnvironmental Exposure

A variety of occupational and environmental exposures have been implicated in the pathogenesis of lung cancer.

These include asbestos and silica fibers, organic compounds such as chloral methyl ether and PAHs, diesel fumes and air pollution, metals such as chromium and nickel, arsenic, and ionizing radiation. Assessment of risk related to individual occupational/environmental factors is difficult because of imprecise methodologies for quantifying prolonged low-level exposure, the latency between exposure and cancer, and exposure to other factors such as smoking, which confound the analysis . In general, cigarette smoking potentiates the effects of many occupational/environmental carcinogens. These issues are comprehensively reviewed in several recent articles. Numerous studies have demonstrated a significant increase in lung cancer risk in individuals with occupational exposure to asbestos or silica.

All of the common types of commercial asbestos have been associated with lung cancer, with an apparent dose-response relationship and a long latency period. Smokers with lung cancer have higher pulmonary asbestos levels compared to nonsmokers with lung cancer, a phenomenon that might explain the multiplicative effects of cigarette smoking and asbestos on lung cancer risk. Lung cancer risk increases with cumulative exposure to silica. However, unlike asbestos, silica exposure does not appear to exhibit multiplicative effects with smoking.

7.3. PATHOLOGY

The designation non-small cell carcinoma of the lung refers to a large group of disparate pulmonary neoplasms that are often associated with cigarette smoking and share the common property of being less responsive to small cell carcinoma treatment protocols. Through the 1960s, the predominant type of NSCLC was squamous cell carcinoma, but adenocarcinoma has increased in both relative and absolute incidence, a phenomenon that has been temporally associated with changes in tobacco blends and the use of filters on cigarettes.

Adenocarcinoma

The shift to adenocarcinoma has changed the clinical presentation and means of detection of early stage NSCLC. Nearly all adenocarcinomas arise in the smaller airways histologically, and can be detected radiographically, especially with computed tomography (CT) scan, in the periphery of the lung. They are less likely to present with cough and hemoptysis, and are less amenable to detection by sputum cytology or bronchoscopy, but more accessible to CT-guided fine-needle aspiration (FNA). The 2004 World Health Organization (WHO) Histologic Typing of Lung Cancers recognizes 14 subtypes of adenocarcinoma of the lung, but only a few types account for the great majority of cases. Most adenocarcinomas of the lung immunostain in the nucleus for thyroid transcription factor-1 and in the cytoplasm for carcinoembryonic antigen.

The histologic precursor to pulmonary adenocarcinoma is considered to be atypical adenomatous/alveolar hyperplasia (AAH). Typically found incidentally in pulmonary specimens removed for other, more advanced, neoplasms, AAH measures less than 5 mm in diameter, and is composed of atypical type II pneumocytes proliferating on an alveolar wall that is either normal in thickness or altered by inactive fibrous scarring. There is a histologic spectrum between AAH and small nonmucinous bronchioloalveolar carcinoma (BAC), and these neoplasms are difficult to differentiate in small samples by cytologic, histologic, and genetic techniques. Lesions 5 mm in diameter or less are usually made up of relatively small cells with limited nuclear atypia in comparison to larger lesions, which exhibit correspondingly greater degrees of pleomorphism.

The frequency and rate of progression of AAH to adenocarcinoma is uncertain, but considered to be low.

Bronchioloalveolar Carcinoma

BAC is a term that has been used loosely over the years, but the 1999 WHO Classification of Lung Tumors specified BAC as a noninvasive carcinoma spreading on the surface of alveolar walls without invasion. It is found in mucinous and nonmucinous variants. Mucinous BAC is an unusual variant characterized by the presence of malignant mucus-containing goblet cells on the surface of normal alveolar walls; it has a tendency to be multifocal or to spread through the airways and carries a high mortality rate. Nonmucinous BAC is much more commonly found, is composed of type II pneumocytes or Clara cells exhibiting nuclear anaplasia and pleomorphism greater than AAH, but less than invasive adenocarcinoma. The malignant cells spread over the alveolar walls in a monolayer, which presents a barrier to gas exchange in the affected alveolar sac, leading to right to left intrapulmonary shunt.

Although relatively uncommon, BACs have been the focus of intense research during recent years. These cancers, particularly those arising in nonsmoking females of Asian descent, exhibit unique epidermal growth factor (EGFR) mutations that confer exquisite sensitivity to EGFR-tyrosine kinase inhibitors (EGFR-TKI) such as erlotinib and gefitinib. Early-stage peripheral adenocarcinomas have also been studied and reported as having a good prognosis. Noguchi et aJ. l lO reported five different subtypes (A through E) of small, stage I adenocarcinomas.

In type A, BAC proliferates on the alveolar surface of essentially normal alveolar walls, whereas in type B, alveolar walls are scarred with well-established collagen or elastotic fibers, which are considered evidence of parenchymal collapse, but they are free of proliferating fibroblasts. Types A and B were associated with a 100% survival rate and are considered noninvasive or carcinoma in situ, and therefore incapable of metastasizing because they have not invaded the stroma or angiolymphatic vessels of the lung.

Their lepidic growth pattern, however, allows for spread within the airways. When invasive carcinoma is present, the term BAC should not be used. Thus defined, BAC is an uncommon type of adenocarcinoma of the lung.

However, a BAC pattern is much more often seen at the periphery of invasive types of adenocarcinoma in a mixed subtype, which includes acinar (gland-forming), papillary, and solid patterns. Vazquez et al. named these mixed carcinomas as type C, with the discriminating feature of a desmoplastic stroma, considered evidence of invasion. Five-year mortality rates for patients with Noguchi type C adenocarcinomas approximate 20%, indicating a capacity of these neoplasms to invade angiolymphatic spaces, and to metastasize to lymph nodes and other sites. Types D and E adenocarcinomas have progressively higher nuclear and histologic grades in an invasive stroma and correspondingly higher mortality rates. Other authors have confirmed this work. Adenocarcinomas with a predominant BAC pattern, but limited areas of invasion also have a good prognosis, analogous to microinvasive carcinomas described in other organs.

Fetal adenocarcinomas are rare tumors that resemble the developing lung in the pseudoglandular period and are characterized by primitive bronchilike structures lined by columnar cells with subnuclear vacuoles rich in glycogen. Three other subtypes of primary pulmonary adenocarcinoma stress the ever-present differential diagnosis of primary from metastatic adenocarcinoma. Primary mucinous adenocarcinomas are composed of goblet cells and may mimic colon cancers both histologically and immunohistochemically; signet ring carcinomas with single cells and small groups withanaplastic nuclei and eccentric intracellular vacuoles of mucous resemble gastric carcinomas.

Clear cell carcinoma with centrally placed nucleus in a clear cytoplasm may be mistaken for renal cell carcinoma. Distinctions are often made on clinical grounds with recognition of a prior or concurrent extrapulmonary carcinoma, and may be aided by the use of immunohistochemical staining. lmmunostains for carcinoembryonic antigen, BER EP4, MOC31, and B72. 3 are usually positive in adenocarcinomas of the lung, but fail to distinguish primary lung cancer from primaries in other organs . The antibody to thyroid transcription factor- 1 and cytokeratin 7 (CK7) are useful as markers of origin for adenocarcinomas in the lung (or thyroid), whereas CK20 antigen is characteristic of adenocarcinomas of the gastrointestinal tract (especially colon), and GCDFP-15 is observed in breast cancers. Poorly differentiated adenocarcinomas are composed of a solid type of large cell carcinoma in which mucin production is limited and can only be demonstrated with the aid of histochemical stains. Differential diagnosis in these lesions is between adenocarcinoma and undifferentiated carcinoma of the lung or other organs.

Large Cell Carcinoma

Large cell carcinomas are composed of large cells that are similar in many ways to those of an adenocarcinoma or a squamous cell carcinoma, but the cytoplasm lacks the differentiating features of mucin production or dense keratinization and the cells form no glandular structures . They account for approximately 15% of all lung cancers . With extensive sampling and electron microscopy, many large cell carcinomas can be classified appropriately as poorly differentiated adenocarcinoma or, less often, squamous cell carcinoma.

Although the WHO classification recognizes basaloid, lymphoepithelioma-like, and clear cell types, they differ little in clinical presentation or course, and in most clinical trials, large cell carcinoma and adenocarcinoma are grouped together.

Squamous Cell Carcinoma

Squamous cell carcinoma may present clinically in the periphery of the lung as a small subpleural nodule with the radiographic appearance and overall prognosis of a peripheral adenocarcinoma, but squamous cell carcinoma classically arises in proximal (segmental or larger) bronchi via progression through stages of dysplasia. In its earliest form (carcinoma in situ), malignant squamous cells spread over the bronchial surface, and may involve submucosal glands. Because there is exfoliation of the malignant cells from the bronchial surface, squamous cell carcinoma can rarely be detected by cytologic examination in an occult stage before it is evident on chest radiograph because of its origin in the large and dense proximal bronchi. With further growth, squamous cell carcinoma invades the basement membrane and extends into the parenchyma and bronchial lumen, producing obstruction with resultant atelectasis or pneumonia. Histologically, squamous cell carcinoma is composed of sheets of epithelial cells with individual cell keratinization, intercellular bridges, and/or pearl formation. Squamous cell carcinoma tends to be slowgrowing; it is estimated that the progression of in situ carcinoma to a clinically apparent tumor takes 3 to 4 years. Because of the proximal location and growth pattern, surgical resection may be compromised and local failure in the chest is more common. Most squamous cell carcinomas immunostain in the nucleus for p63 and in the cytoplasm for CKS/6.

Adenosquamous Carcinomas

Adenosquamous carcinomas have histologic areas differentiated as both squamous cell carcinoma and adenocarcinoma, are predominantly found in the periphery of the lung, and have clinical behavior much like that of adenocarcinoma. However, studies suggest that they are a cytogenetically distinctentity.

Pleomorphic Carcinomas

This grouping of tumors includes carcinomas with giant and usually multinucleated cells, or with spindle cell, pseudosarcomatous configuration, and those with both carcinoma and sarcoma morphology, including the rare pulmonary blastoma. All are aggressive malignancies, and typically are advanced when diagnosed; survival is stage-dependent.

Carcinomas of Salivary Gland Type

These tumors are predominantly found in large bronchi and thought to arise from submucosal gland epithelium. Mucoepidermoid carcinomas are recognized by their characteristic intermediate or transitional cells and are divided into low grade and high grade, based on nuclear morphology and degree of squamous cell differentiation. Mortality rates have been reported as distinctly worse for the high-grade mucoepidermoids in some series. Adenoid-cystic carcinomas share the aggressiveness of their salivary gland counterparts. Rare lowgrade, acinic cell carcinomas have been reported.

Carcinoids

These neoplasms manifest a prominent neuroendocrine phenotype in morphology, immunohistochemistry, and ultrastructure.

Histology is characterized by insular, ribbon or festoon, pseudorosette, and sometimes spindle cell patterns of cuboidal cells with small and hyperchromatic nuclei. Immunohistochemically, they are usually positive for synaptophysin, chromogranin A, and/or CD56 and ultrastructurally, they contain dense core granules. Typical carcinoids are usually found in large bronchi and most often feature an organoid pattern. Peripheral carcinoids are often spindle-cell tumors, which may be mistaken for metastatic sarcomas, especially of the endometrial stroma.

7.4. CLINICAL PRESENTATION

The signs and symptoms manifested by patients suffering from lung cancer depend on the histology of the tumor and the extent of locoregional invasion, as well as the location, size, and number of distant metastases. Many patients present with an asymptomatic lesion discovered incidentally on chest radiography or CT scan.

Tumors arising in the larger airways may cause persistent cough, wheezing, or hemoptysis. Typically, patients with hemoptysis experience blood-streaked sputum; massive bleeding is rarely seen at presentation. Continued growth of endobronchial tumors frequently results in atelectasis with or without pneumonia and abscess. Pleural involvement by tumor or associated infection may cause pleuritic pain with or without effusion. Diminished lung function may result in dyspnea, the severity of which depends on the amount of lung involved and the patient's underlying pulmonary reserve.

Tumors invading the chest wall typically produce either stabbing or burning radicular pain with or without pleural effusion. Tumors arising within the superior sulcus may be associated with a classic Pancoast syndrome from invasion of the lower brachial plexus (T1 and C 8 nerve roots), stellate ganglion, and chest wall or vertebral bodies. Invasion or encasement of structures within the mediastinum may cause superior vena cava (SVC) syndrome, recurrent or phrenic nerve palsy, esophageal dysphagia, tracheoesophageal fistula, or pericardia! effusion. In addition to experiencing specific symptoms directly related to the tumor or associated lymphadenopathy, many patients complain of vague chest discomfort, which is usually of visceral origin. Nearly all patients with advanced NCSLC exhibit symptoms referable to their disease on initial presentation. Fatigue and decreased activity are reported by more than 80% of individuals, and most patients also experience cough, dyspnea, anorexia, and weight loss. The presenting complaints of patients with metastatic disease are largely determined by the specific sites involved, such as bone, brain, liver, and adrenal glands. In addition, patients may exhibit a variety of paraneoplastic syndromes, which may improve following treatment of the underlying malignancy.

7.5. TNM-CLASSIFICATION

T – Primary Tumour

TX   Primary tumour cannot be assessed, *or* tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0   No evidence of primary tumour

Tis   Carcinoma in situ

T1   Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[1]

T1a   Tumour 2 cm or less in greatest dimension[1]

T1b   Tumour more than 2 cm but not more than 3 cm in greatest dimension[1]

T2   Tumour more than 3 cm but not more than 7 cm; or tumour with any of the following features[2]
- Involves main bronchus, 2 cm or more distal to the carina
- Invades visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a   Tumour more than 3 cm but not more than 5 cm in greatest dimension

T2b   Tumour more than 5 cm but not more than 7 cm in greatest dimension

T3   Tumour more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; *or* tumour in the main bronchus less

than 2 cm distal to the carina1 but without involvement of the carina; *or* associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe as the primary

T4 Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M – Distant Metastasis

M0 No distant metastasis

M1 Distant metastasis

M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion[3]

M1b Distant metastasis

Notes: 1. The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

2. T2 tumours with these features are classified T2a if 5 cm or less, or if size cannot be determined and T2b if greater than 5 cm but not larger than 7 cm.

3. Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopical examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

Stage grouping			
Stage	T	N	M
Occult carcinoma	Tx	N0	M0
0	Tis	N0	M0
IA	T1a	N0	M0
	T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
IIB	T2b	N1	M0
	T3	N0	M0
IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T4	N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1

7.6. DIAGNOSTICS

Sputum Cytology

Cytologic analysis of exfoliated cells in sputum is a rapid, relatively inexpensive means to establish a tissue diagnosis in an individual with an apparent pulmonary carcinoma. Sputum can be either spontaneously collected or induced with hypertonic saline; three daily pooled specimens increase the diagnostic yield. Sputum samples are considered representative if alveolar macrophages as well as bronchial epithelial cells are present. Previous reports have indicated that the sensitivity of sputum cytology is 65% (range 22% to 98%) in the setting of established cancers. The diagnostic yield of sputum cytology is enhanced in the context of centrally located lesions, squamous cell carcinomas, and large tumors, particularly if multiple sputum samples are examined.

A variety of molecular techniques have been evaluated as a means to increase the diagnostic yield of sputum cytology. These include nuclear image analysis, immunohistochemical evaluation of p53, and heterogeneous nuclear riboprotein A2/B1 expression, analysis of k-ras and p53 mutations, as well as loss of heterozygosity, aberrant promoter methylation, and DNA adduct levels in genomic DNA. Additional studies have focused on the evaluation of automated sputum cytology techniques and analysis of gene or microRNA expression profiles in exfoliated tumor cells. Overall, the feasibility and efficacy of these newer methodologies in the context of sputum cytology for detection of occult pulmonary malignancies, particularly peripheral adenocarcinomas and monitoring treatment responses in established carcinomas, have yet to be determined.

Percutaneous Fine-Needle Aspiration

FNA is an excellent method for establishing tissue diagnosis of pulmonary nodules. This can be performed using fluoroscopic or CT-guided techniques. The positive yield in experienced hands exceeds 95% even if lesions are less than 1 cm in diameter. Indeterminate biopsies must be interpreted with caution; FNA cannot rule out malignancy unless a true/positive benign diagnosis (i.e., hematoma or infectious process) is definitively established.

Abnormalities involving bone, liver, and adrenal glands, suggestive of metastatic disease on staging studies, can be readily confirmed by FNA using ultrasonographic or CT-guided techniques. Frequently, biopsy of one of these sites simultaneously establishes tissue diagnosis and stage of disease.

Bronchoscopy

Fiberoptic bronchoscopy (FOB) can be performed with or without sedation, and with minimal morbidity and exceptional safety. FOB enables visualization of the tracheobronchial tree to the second or third segmental divisions; cytologic In general, the diagnostic yield of FOB with cytologic brushings or biopsy of visible lesions exceeds 90%. Even when no visible lesion is identified, the bronchus draining the area of suspicion can be lavaged, and effluent obtained for cytologic analysis. With the use of FOB combined with fluoroscopy or CT imaging techniques, peripheral lesions can be reached by cytology brushes, needle, or biopsy forceps.

FOB also be used to evaluate hilar and mediastinal lymph nodes; transbronchoscopic needle aspiration through the airway wall, particularly when used in conj unction with endoscopic bronchial ultrasound (EBUS) techniques, can confirm the presence of malignancy in enlarged hilar or mediastinal lymph nodes without the need for mediastinoscopy, thoracoscopy, or EUS/FNA.

Two recent prospective studies have demonstrated sensitivities of 77% to 87% versus 68% to 85% and negative predictive values of 78% to 86% versus 59% to 90% for EBUS-FNA and cervical mediastinoscopy (CME), respectively.

Of note, the negative predictive value of EBUS-FNA needs to be confirmed in additional large studies. Several recent studies have evaluated the sensitivity and accuracy of EBUS-FNA for restaging the mediastinum following induction therapy in lung cancer patients. A retrospective study involving 61 consecutive patients with confirmed stage IIIA/N2 disease who underwent induction chemotherapy followed by EBUS-FNA and extended ME, revealed sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of restaging EBUS-FNA procedures of 67%, 86%, 80%, 91%, and 78%, respectively. In contrast, evaluation of 124 consecutive patients with stage IIIA/N2 NSCLC treated with induction chemotherapy revealed that 28 of 35 patients with no apparent mediastinal nodal disease by EBUSFNA had residual N2 lymph node metastases at thoracotomy; the vast maj ority of these false-negative results were due to sampling rather than detection errors . The overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 76%, 100%, 100%, 20%, and 77%, respectively.

These data suggest that given the potentially low negative predictive value, EBUS-FNA may not be a reliable means of confirming sterilization of mediastinal lymph node metastases following induction therapy in lung cancer patients.

Endoscopic Ultrasound-FineNeedle Aspiration

EUS-FNA is a minimally invasive and safe means to assess subcarinal (station 7) lymph nodes typically biopsied by CME or transbronchial techniques, and lower mediastinal lymph nodes (stations 8 and 9) that are not accessible via standard CME.

Meta-analysis of 18 studies revealed that EUS-FNA correctly identified 83% and 97% of patients with positive and negative mediastinal lymph nodes, respectively. Sensitivity and specificity were 90% and 97%, respectively, for patients with abnormal mediastinal lymph nodes on CT scans. Sensitivity was 58% for patients without mediastinal lymphadenopathy. More recent analysis revealed that EUS-FNA has sensitivity, negative predictive value, and accuracy of 74%, 73%, and 85%, respectively, for N2/N3 disease; these values increase to 92%, 85%, and 85%, respectively, when EUS-FNA is combined with CME. EUS-FNA can reduce the number of patients requiring CME for documentation of mediastinal metastases, and decrease the number of patients undergoing potentially unwarranted thoracotomy

Mediastinoscopy /Mediastinotomy, and Thoracoscopy

CME remains the most accurate technique to assess paratracheal (stations 2, 3, and 4), proximal peribronchial (station 10), and subcarinal (station 7) lymph nodes in lung cancer patients. This procedure is very safe in experienced hands. Mediastinoscopy is indicated in any patient suspected of having locally advanced disease on the basis of direct tumor extension to the mediastinum, enlarged lymph nodes on CT scan, or mediastinal uptake on PET scan.

Lymph nodes within the aortopulmonary window and along the ascending aorta (stations 5 and 6) are not accessible by standard mediastinoscopy techniques; however, these stations can be evaluated by extended mediastinoscopy, anterior mediastinotomy, EUSFNA, or video-assisted thoracoscopic techniques.

The role of mediastinoscopy before surgical intervention for lung cancer has evolved during recent years, particularly in light of data pertaining to adj uvant chemotherapy in patients with completely resected neoplasms . With mediastinoscopy, inoperable supraclavicular or contralateral mediastinal (N3) disease can b e identified, thereby avoiding unnecessary thoracotomies.

Currently, it is reasonable to forgo mediastinoscopy in patients with clinical stage I disease, particularly those with PET-positive tumors but no mediastinal tracer uptake, given the high negative predictive value of FDG-PET scans. However, any patient entering a prospective trial should undergo mediastinoscopy (or other invasive procedure) for definitive staging of their tumor. Furthermore, patients with more locally advanced disease (clinical stage II or III), particularly those potentially requiring pneumonectomy, should undergo mediastinoscopy to rule out N3 disease, and to identify those individuals with N2 disease for whom induction therapy should be considered prior to surgery.

Several studies have examined the feasibility and safety of CME for mediastinal restaging following induction therapy in potentially resectable patients. Sensitivity of CME in this setting ranges from 30% to 70%; fibrosis resulting from prior CME or induction therapy may limit the number of nodal stations accessible on repeat CME. Two recent prospective studies have demonstrated sensitivity of 77% to 87% versus 68% to 85% per EBUS-FNA and CME, respectively, and a negative predictive value of 78% to 86% versus 59% to 90% for EBUS versus CME.

Presently, a reasonable approach for patients with high likelihood of requiring induction therapy prior to surgery is to use EBUS-FNA or EUS-FNA techniques to initially stage the mediastinum with the caveat that a negative EBUS-FNA will need confirmation by other more invasive techniques; CME should be performed prior to resection to accurately assess response to therapy.

Video-assisted thoracoscopic surgery (VATS) is frequently used for the diagnosis, staging, and resection of lung cancer. Peripheral nodules can be identified and excised using videoassisted, minimally invasive techniques, and mediastinal lymph nodes can be sampled for histologic examination. VATS is also extremely useful for evaluation and palliation of suspected pleural disease, particularly when thoracentesis has been nondiagnostic.

Thoracoscopy is ideal for assessment of mediastinal nodes not accessible by standard mediastinoscopy or EUSFNA techniques, and for evaluation of suspected T4 lesions .

Thoracentesis

Needle drainage of a pleural effusion associated with a presumed lung cancer can identify inoperable, pleural disease (M1a). Typically, a bloody pleural effusion is malignant; however, unless malignant cells are identified, a bloody pleural effusion should be considered traumatic. In general, a diagnosis of cancer can be established in 70% of malignant effusions by thoracentesis. If the initial thoracentesis is negative, additional percutaneous thoracenteses improve the diagnostic yield; otherwise, thoracoscopy can be used to simultaneously collect pleural fluid for cytologic examination, and obtain pleural as well as lymph node biopsies for tissue diagnosis.

Thoracotomy

Typically, more than 95% of tumors can be accurately diagnosed and staged prior to thoracotomy. Nevertheless, in a small minority of cases, the diagnosis of lung cancer is made only at thoracotomy. In general, these are cases in which there is a large, inflammatory component associated with a small focus of cancer that obscures diagnosis. During thoracotomy the diagnosis often can be obtained via multiple FNAs with immediate cytologic analysis, or incisional (or preferably excisional) biopsy with frozen section. Additional intraoperative biopsies of hilar and mediastinal lymph nodes should be obtained with resection of the primary lesion and complete mediastinal lymph node dissection performed, if indicated on the basis of intraoperative staging.

Lung Cancer Screening

Considerable efforts have focused on the evaluation of sputum cytology, chest radiographs, and more recently, screening CT scans for early detection of lung cancer. Whereas previous trials using sputum cytology and/or chest radiographs were negative, recent studies suggest that serial CT scans are useful for early detection of early-stage lung cancers, and have the potential of reducing lung cancer-specific mortality in highrisk individuals. However, results of large randomized studies are still eagerly awaited.

Chemoprevention

Despite encouraging preclinical data, the results of large chemoprevention trials evaluating primary prevention (healthy highrisk smokers), secondary prevention (premalignant lesions) , and tertiary prevention (second primary tumors in previously treated individuals) have been disappointing. Well-designed phase 2 or phase 3 trials have failed to demonstrate efficacy of retinoids including retinal, retinal palmitate, isotretinoin, or carotene, for primary, secondary, or tertiary prevention of lung cancer. Vitamin E (a-tocopherol) or selenium supplements do not appear to be affective chemopreventive agents.

Recent data indicate that erbB1/erbB2, ras, cox-2, AKT, and PB -kinase signaling modulate growth and metastasis of lung cancer cells171; as such, inhibitors of these pathways are attractive agents for evaluation in lung cancer prevention trials.

A variety of drugs targeting these aforementioned signaling abnormalities, as well as DNA demethylating agents and histone deacetylase inhibitors, prevent lung cancers in mice exposed to tobacco carcinogens. The efficacy of these compounds alone or in combination for chemoprevention of human lung cancers has not been established.

7.7. TREATMENT

Surgery

Surgery remains the best treatment modality for patients whose lung cancers are limited to the hemithorax and can be totally encompassed by excision. In stage I and stage II disease, when the tumor has not extended beyond the bronchopulmonary lymph nodes, complete (RO) resections are almost always feasible. Currently, controversy arises regarding the management of N2 disease. Ipsilateral N2 mediastinal lymph node involvement, despite being potentially resectable, typically portends limited survival following surgery alone.

Historically, patients in whom N2 disease is identified preoperatively have a much poorer prognosis than individuals with occult N2 disease discovered at the time of thoracotomy (<10% vs. 30% 5-year survival rates, resp ectively). Randomized trials indicate that combined-modality approaches using either induction (preoperative) or adj uvant chemotherapy with or without radiation improves survival in patients with resectable stage IIIA lung cancers. In general, stage IIIB lung cancers, by virtue of contralateral (N3) lymph node metastases or invasion of vital structures such as carina, heart, or great vessels (T4), particularly in the presence of N2 disease are inoperable. Similarly, lung cancers that are associated with malignant pleural effusion or presence of contralateral nodules (M1a), or have metastasized to distant organs (M1b) are generally incurable by surgery; however, individuals with oligometastases involving brain or adrenal gland occasionally experience long-term survival following resection of the primary and metastatic lesions.

Surgical Procedures

Lobectomy is currently the standard of care, providing this will result in complete resection of the tumor mass. If the tumor extends across a fissure, lobectomy with en bloc segmentectomy, bilobectomy, or pneumonectomy should be performed if the patient can tolerate a larger resection. Recently, there has been a resurgence of interest in smaller resection for early-stage nodenegative carcinomas. For proximally situated (T3) tumors, parenchymal-preserving operations using bronchoplastic or angioplastic techniques should be performed whenever possible, as patients undergoing these resections have comparable survival rates and improved quality of life relative to patients with similarly staged tumors undergoing pneumonectomy.

The most common complications after lung cancer surgery are not related to technical failures of the operation, but rather are due to cardiopulmonary issues, particularly supraventricular arrhythmias and respiratory failure. Because of improved surgical and anesthetic techniques and perioperative care, postoperative mortality rates for surgical resection for lung cancer patients have decreased remarkably during the past 50 years. Presently, pneumonectomy can typically be performed with a mortality rate of less than 6%, lobectomy less than 3%, and smaller resections with 1% or less. Kozower e t al. Used the Society of Thoracic Surgeons database containing 18,800 lung cancer resections performed at 100 centers between January 1, 2002, and June 30, 2008, to develop three multivariate risk models (major morbidity, mortality, and combined maj or morbidity/mortality) . The overall perioperative mortality rate was 2.2%; the composite major morbidity/mortality rate was 8.6%. Significant predictors of mortality included pneumonectomy or bilobectomy, performance status, American Society of Anesthesiologists score, induction chemoradiation therapy, age, steroids, male gender, FEVh body mass index, and urgent procedures.

Radiation Therapy
Techniques

External-beam radiation therapy consists of high-energy photon beams generated by a linear accelerator or proton beams generated by a cyclotron. Therapeutic doses of radiation must be delivered to the target while minimizing incidental irradiation of surrounding normal tissues . A planning session is necessary before treatment can begin. This process typically requires a planning CT scan with the patient in the treatment position, often in an immobilization device to limit day-to-day setup errors. The radiation oncologist defines the target and surrounding normal tissues on the CT images using special treatmentplanning software. New imaging modalities such as FDG-PET can be helpful in discriminating between tumor and atelectasis, and involved versus uninvolved lymph nodes. A three-dimensional (3D) map is constructed, which delineates the location of the target and normal surrounding organs. A treatment plan is then developed. This involves choosing beam orientations, the number of beams, energy, and weighting. Multiple plans can be compared using dose-volume histograms, which display the dose received by the target and critical structures. Photon energies between 4 and 10 MV are preferred for patients with peripheral tumors surrounded by low-density lung parenchyma, given dose build-up issues at the interface of the lung and tumor. Higher-energy photons (15-18 MV) may be necessary for optimal dose homogeneity in larger patients or when oblique fields are utilized.

Respiratory Motion

Lung tumors, especially peripheral tumors in the lower lobes, invariably move during the respiratory cycle. This motion must be taken into account during the planning process. Multiple methods, some simple and others more complex, are available to manage respiratory motion. One approach is to determine the motion trajectory of the tumor during the respiratory cycle and design radiation fields that encompass this entire volume.

This includes such methods as slow CT scanning during quiet respiration, obtaining a breath-hold CT in inspiration and expiration and combining these volumes, obtaining a fourdimensional CT (4D CT), and creating a maximum-intensity projection dataset. The magnitude of respiratory motion can be dampened using an abdominal compression device.

Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) is a relatively new radiation delivery technique in which the fluence of individual beams is modulated to allow better conformality of the high-dose volume to the target. Dose to adjacent normal structures is not eliminated with IMRT, rather it is redistributed. In fact, IMRT increases the volume of lung receiving a low dose of RT, and may actually increase the rate of injury. Furthermore, because IMRT is typically delivered using moving multileaf collimators, where each region of the field is not treated simultaneously, one needs to be careful to consider the possible confounding impact of respiratory motion on IMRT dose delivery. Under clinical circumstances when IMRT is deemed necessary (e.g., when avoidance of critical structures such as the spinal cord cannot be accomplished using standard radiation fields) several factors must be explicitly addressed. Assessment of tumor motion, ideally with a 4D CT scan, is mandatory. The target volumes and surrounding organs at risk must be contoured and appropriate constraints placed to both adequately treat the tumor and minimize dose to critical surrounding structures. Procedures must be put in place to verify accurate patient-setup prior to treatment. This may include kilovolt onboard imaging, cone beam CT, or (at a minimum), verification of the isocenter weekly using megavoltage portal images. Finally, quality assurance measurements of the IMRT plan should be performed.

Chemotherapy

Platinum-based combinations have become the standard of care for treating unselected advanced NSCLC, and chemotherapy has been advocated as an integral part of combined modality approaches to earlier stages of disease. In 1988, Rapp et al. reported that cisplatin-based chemotherapy improved survival of patients with advanced NSCLC. Several additional trials comparing chemotherapy versus best supportive care (BSC) have confirmed these findings, prompting widespread use of chemotherapy for palliation in patients with advanced disease.

Cisplatin- or carboplatin-based doublets (in combination with paclitaxel, gemcitabine, pemetrexed, docetaxel, or vinorelbine) are now standard for patients with stage IV disease.

Recently, EGFR tyrosine kinase inhibitors have been introduced in second- and third-line treatment of advanced disease and in selected patients in first-line treatment. Recent evidence indicates that p atients who have an activating mutation of EGFR benefit more from an EGFR inhibitor than from chemotherapy in first-line treatment of advanced disease.

Chemotherapy also improves outcome for patients with locoregional disease. When used either in sequence or concurrently with radiation, platinum-based therapy prolongs survival and increases the fraction of patients with stage III disease who are long-term survivors. Whereas some of this benefit may be the result of improved local control, eradication of micrometastatic disease appears to be the principal mechanism by which chemotherapy improves survival of patients with locally advanced lung cancer.

Neoadjuvant (induction) chemotherapy, in which a specified number of cycles are administered before definitive local therapy with surgery or radiation, appears to be beneficial in patients with locally advanced NSCLC. The simultaneous use of chemotherapy and RT (concomitant chemoradiotherapy) has also been intensively investigated. In theory, adj uvant and induction chemotherapy are administered t o improve control of occult metastatic disease. Decreasing the size (downstaging) of the locoregional tumor burden may also be observed after induction therapy. The delay of RT to allow administration of induction chemotherapy has been of theoretic concern because this could lead to the proliferation of clonogenic tumor cells in an unresponsive tumor. Concomitant chemoradiotherapy also results in systemic antitumor activity. However, this will be realized only if systemically active doses and schedules of the drugs are administered. In clinical practice, the latter has been challenging because radiation-related toxicities (i.e., esophagitis and radiation pneumonitis) are usually increased in the presence of chemotherapy. Therefore, the primary goal of concomitant chemoradiotherapy should be to enhance the antitumor activity of radiation and increase locoregional control (radiation sensitization or enhancement).

Induction chemotherapy followed by RT prolongs the overall survival in patients with unresectable stage III disease compared with patients receiving RT alone. Trials by Furuse et al. and the RTOG support the use of concurrent chemotherapy and radiation compared with sequential chemotherapy when treating locally advanced disease. However, the toxicity of concurrent chemoradiotherapy is substantial, and for patients with an impaired performance status, sequential chemotherapy and radiation is preferable.

Chemotherapy has an emerging role in stage IIIA (N2) disease. The use of induction chemotherapy in the surgical setting (stage IIIA) alone or in conjunction with RT, results in a 5-year survival of 20% to 30% compared with 5% to 10% for surgery alone for clinical N2 disease. Intergroup data indicated a significant increase in progression-free survival in patients treated with chemoradiotherapy followed by surgery, but the anticipated improvement in survival of 10% was not evident.

Before 2003 there was little evidence to support the routine use of adj uvant chemotherapy after potentially curative resections in lung cancer patients. Several large randomized studies now support the use of adj uvant cisplatin-based chemotherapy in radically resected stage II and IIIA NSCLC.

7.8. QUESTIONS FOR SELF-CONTROL
1. What place does lung cancer take in the structure of oncological diseases? Give a characteristic of it.
2. What is the incidence of lung cancer in the industrial counries?
3. At what age is the lung cancer diagnosed more frequently?
4. Name two main morphological forms of lung cancer.
5. What is the pathogenesis of central lung cancer?
6. Enumerate the most often paraneoplastic syndromes at the small-cell lung cancer.
7. Enumerate the symptoms related to intrathoracic spread of the tumour at the small-cell lung cancer.
8. Give a characteristic of the limited-stage of the small-cell lung cancer.
9. Give a characteristic of the extensive-stage of the small-cell lung cancer.
10. What method of treatment is the main at the small-cell lung cancer?
11. How does lung cancer spread?
12. What is the main x-ray symptom of the central lung cancer?

7.9. TESTS FOR SELF-CONTROL
1. Lung cancers occur with increased frequency in:
    a. Non-smokers
    b. Heavy drinkers
    c. Uranium miners
    d. Architects, engineers and policemen
2. Small-cell lung cancers account for 70-75% of all lung cancers:
    a. True
    b. False
    c. May be
    d. None of the above
3. The most common cause of superior vena-cava obstruction is:
    a. AIDS
    b. Inflammatory Bowel-disease

       c. Myocardial infarction
       d. Lung cancer
4. A Pancoast tumour is generally located:
       a. Bilaterally
       b. In the superior sulcus of the lung apex
       c. In the left lung
       d. In the subsegmental bronchus
5. Exposure to ……… has been strongly associated with all lung cancers:
       a. Asbestos dust
       b. UV Radiation
       c. Pollution
       d. All of the above

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

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THEME 8

UTERINE, CERVICAL AND OVARIAN CANCER

CANCER OF THE CERVIX
8.1. EPIDEMIOLOGY

The American Cancer Society estimated that in the United States in 2010, 12,200 new cases of invasive cervical cancer would be diagnosed and there would be 4210 deaths due to cervical cancer, representing approximately 1.5% of all cancer deaths in women. In the United States and other developed countries, age-adjusted death rates from cervical cancer have declined steadily since the 1930s. Although this improvement is primarily the result of the adoption of routine screening programs, the death rates from cervical cancer had begun to decrease before the implementation of Papanicolaou (Pap) screening, suggesting that other, unknown factors may have played some role.

International incidences of cervical cancer tend to reflect differences in cultural attitudes toward sexual promiscuity and differences in the penetration of mass screening programs. The highest incidences tend to occur in populations that have low screening rates combined with a high background prevalence of human papilloma virus (HPV) infection and relatively liberal attitudes toward sexual behavior. Rates of invasive cervical cancer are particularly high in Latin America, southern and eastern Africa, India, and Polynesia; in many of these developing countries, cervical cancer is the leading cause of cancer deaths among women. Differences in age-specific incidences between developed and medically underserved countries illustrate the probable impact of mass screening on the development of invasive disease. For example, a comparison between data from Brazil and the United Kingdom showed similar rates of cervical cancer in young women, suggesting similar levels of exposure to HPV, but rapidly diverging rates in older women, probably reflecting differences in the availability of mass screening in the two countries.

Although the overall incidence of cervical cancer is low in the United States, the incidence in black Americans is about 30% higher than the incidence in white Americans, and the incidence in Hispanic women is about twice the incidence in white Americans. Barriers to cervical cancer screening, including lack of insurance, low income, and cultural factors, probably contribute to higher incidences and mortality rates in black and Hispanic women.

8.2. ETIOLOGY, RISK FACTORS

Risk factors
- obesity - the larger the woman, the larger the risk
- high levels of estrogen
- endometrial hyperplasia
- hypertension
- polycystic ovary syndrome
- nulliparity (never having carried a pregnancy)

- infertility (inability to become pregnant)
- early menarche (onset of menstruation)
- late menopause (cessation of menstruation)
- endometrial polyps or other benign growths of the uterine lining
- diabetes
- Tamoxifen
- high intake of animal fat
- pelvic radiation therapy
- breast cancer
- ovarian cancer
- anovulatory cycles
- age over 35
- lack of exercise
- heavy daily alcohol consumption (possibly a risk factor)

8.3. PATHOLOGY

Cervical Intraepithelial Neoplasia

Several systems have been developed for classifying cervical cytologic findings. Although criteria for the diagnosis of CIN and degree of neoplasia vary somewhat between pathologists, the important features of CIN are cellular immaturity, cellular disorganization, nuclear abnormalities, and increased mitotic activity. If mitoses and immature cells are present only in the lower third of the epithelium, the lesion is usually designated CIN. Lesions involving only the lower and middle thirds are designated CIN2, and those involving the upper third are designated CIN3. The term cervical intraepithelial neoplasia, as proposed by Richart,21 refers only to a lesion that may progress to invasive carcinoma. Although CIN 1 and CIN 2 are sometimes referred to as mild-to-moderate dysplasia, the term CIN is now preferred over dysplasia.

Adenocarcinoma in Situ

Adenocarcinoma in situ is diagnosed when normal endocervical gland cells are replaced by tall, irregular columnar cells with stratified, hyperchromatic nuclei and increased mitotic activity but the normal branching pattern of the endocervical glands is maintained and there is no obvious stromal invasion. About 20% to 50% of women with cervical adenocarcinoma in situ also have squamous CIN. Because adenocarcinoma in situ is frequently multifocal, cone biopsy margins are unreliable. Although some investigators have described a possible precursor lesion termed endocervical glandular dysplasia, the reproducibility and clinical value of this designation are uncertain.

Microinvasive Carcinoma

Microinvasive carcinoma is defined by International Federation of Gynecology and Obstetrics (FIGO) as invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥7 mm. Thus, this diagnosis can be made only after examination of a specimen that includes the entire neoplastic lesion and cervical transformation zone. This requires a cervical cone biopsy. Following the advent of cytologic screening, the proportion of invasive carcinomas that invade less than 5 mm increased more than tenfold to about 20% in the United States.

The earliest invasion appears as a blurring of the stromoepithelial junction with a protrusion of cells into the stroma; these cells are less well differentiated than the adj acent noninvasive cells; have abundant pink-staining cytoplasm, hyperchromatic nuclei, and prominent nucleoli; they also exhibit a loss of polarity at the stromoepithelial junction. Early microinvasion is usually characterized by a desmoplastic response in adjacent stroma with scalloping or duplication of the neoplastic epithelium or formation of pseudoglands (nests of invasive carcinoma that can mimic crypt involvement) . In a study of cone specimens, Reich et al. reported that 12% of microinvasive carcinomas were multifocal. The depth of invasion should be measured with a micrometer from the base of the epithelium to the deepest point of invasion. Lesions that have invaded less than 3 mm (FIGO stage IA1) are rarely associated with metastases; 5% to 10% of tumors that have invaded 3 to 5 mm (FIGO stage IA2) are associated with positive pelvic lymph nodes.

Until FIGO refined its definition of microinvasive carcinoma, most clinicians in the United States used a different definition of microinvasive carcinoma formulated by the Society of Gynecologic Oncologists: cancers that invaded less than 3 mm with no evidence of LVSI. The importance of LVSI remains somewhat controversial; the risk of metastatic regional disease appears to be exceedingly low for any tumor that invades less than 3 mm, even in the presence of LVSI. Although most clinicians have adopted the FIGO definitions, many think that the risk of regional spread from tumors that have invaded 3 to 5 mm is sufficiently high to warrant treatment of the parametria and regional nodes.

Invasive Squamous Cell Carcinoma

Between 80% and 90% of cervical carcinomas are squamous cell carcinomas. Although squamous neoplasms are often subclassified as large cell keratinizing, large cell nonkeratinizing, or small cell carcinomas, these designations do not correlate well with prognosis. Small cell squamous carcinomas have small to medium-sized nuclei, open chromatin, small or large nucleoli, and abundant cytoplasm and are believed by most authorities to have a somewhat poorer prognosis than large cell neoplasms with or without keratin. However, small cell squamous carcinomas should not be confused with the much more aggressive anaplastic small cell neuroendocrine carcinomas discussed later.

Papillary variants of squamous carcinoma may be well differentiated (occasionally confused with immature condylomata) or very poorly differentiated (resembling high-grade transitional carcinoma).

Verrucous carcinoma is a very rare warty-appearing variant of squamous carcinoma that may be difficult to differentiate from benign condyloma without multiple biopsies or hysterectomy. Sarcomatoid squamous carcinoma is another very rare variant, demonstrating areas of spindle-cell carcinomatous tumor confluent with poorly differentiated squamous cell carcinoma; immunohistochemistry demonstrates expression of cytokeratin as well as vimentin. The natural history of this uncommon tumor is not well understood.

Adenocarcinoma

Invasive adenocarcinoma may be pure or mixed with squamous cell carcinoma (adenosquamous carcinoma). About 80% of cervical adenocarcinomas are endocervical-type adenocarcinomas, which are composed predominantly of cells with eosinophilic cytoplasm, brisk mitotic activity, and frequent apoptotic bodies, although many other patterns and cell types have also been observed. Endocervical-type adenocarcinomas are frequently referred to as mucinous; however, although some have abundant intracytoplasmic mucin, most have little or none.

Minimal-deviation adenocarcinoma (adenoma malignum) is a rare, extremely well-differentiated adenocarcinoma that is sometimes associated with Peutz-Jeghers syndrome.38 Because the branching glandular pattern strongly resembles normal endocervical glands and the mucin-rich cells can be deceptively benign-appearing, minimal-deviation adenocarcinoma may not be recognized as malignant in small biopsy specimens. Earlier studies reported a poor outcome for women with this tumor, but more recently, patients have been reported to have a favorable prognosis if the disease is detected early. Glassy cell carcinoma is a variant of poorly differentiated adenosquamous carcinoma characterized by cells with abundant eosinophilic, granular, ground-glass cytoplasm with large round to oval nuclei and prominent nucleoli. Adenoid basal carcinoma is a well-differentiated tumor that histologically resembles basal cell carcinoma of the skin and tends to have a favorable prognosis. Adenoid cystic carcinoma consists of basaloid cells in a cribriform or cylindroma to us pattern; metastases are frequent, although the natural history of these tumors may be long.

Rarely, primary carcinomas of the cervix are composed of endometrioid, serous, or clear cells; mixtures of these cell types may be seen, and histologically, some of these tumors are indistinguishable from those arising elsewhere in the endometrium or ovary. In a study of 17 cases, Zhou et al. found that serous carcinomas of the cervix have an aggressive course, similar to that of high-grade serous tumors originating in the other miillerian sites.

Anaplastic Small Cell/Neuroendocrine Carcinoma

Anaplastic small cell carcinomas resemble oat cell carcinomas of the lung and are made up of small tumor cells that have scanty cytoplasm, small round to oval nuclei, and high mitotic activity; they frequently display neuroendocrine features. Anaplastic small cell carcinomas behave more aggressively than poorly differentiated small cell squamous carcinomas; most investigators report survival rates of less than 50% even for patients with early stage I disease, although recent studies of aggressive multimodality treatments have been somewhat more encouraging. Widespread hematogenous metastases are frequent, but brain metastases are rare unless preceded by pulmonary involvement.

Other Rare Neoplasms

A variety of neoplasms may infiltrate the cervix from adj acent sites, and this makes differential diagnosis difficult. In particular, it may be difficult or impossible to determine the origin of adenocarcinomas involving the endocervix and uterine isthmus. Although endometrioid histology suggests endometrial origin and mucinous tumors in young patients are most often of endocervical origin, both histologic types can arise in either site. Metastatic tumors from the colon, breast, or other sites may involve the cervix secondarily. Malignant mixed miillerian tumors, adenosarcomas, and leiomyosarcomas occasionally arise in the cervix but more often involve it secondarily. Primary lymphomas and melanomas of the cervix are extremely rare

8.4. CLINICAL PRESENTATION

Preinvasive disease is usually detected during routine cervical cytologic screening. Early invasive disease may not be associated with any symptoms and is also usually detected during screening examinations. The earliest symptom of invasive cervical cancer is usually abnormal vaginal bleeding, often following coitus or vaginal douching. This may be associated with a clear or foul-smelling vaginal discharge. Pelvic pain may result from locoregionally invasive disease or from coexistent pelvic inflammatory disease. Flank pain may be a symptom of hydronephrosis, often complicated by pyelonephritis. Patients with very advanced tumors may have hematuria or incontinence from a vesicovaginal fistula caused by direct extension of tumor to the bladder. External compression of the rectum by a massive primary tumor may cause constipation, but the rectal mucosa is rarely involved at initial diagnosis.

8.5. DIAGNOSTICS

The long preinvasive stage of cervical cancer, the relatively high prevalence of the disease in unscreened populations, and the sensitivity of cytologic screening make cervical carcinoma an ideal target for cancer screening.

THEME 8: UTERINE, CERVICAL AND OVARIAN CANCER

In the United States, screening with cervical cytologic examination and pelvic examination has led to a decrease of more than 50% in the incidence of cervical cancer since 1975. Only nations with well-developed screening programs have experienced substantial decreases in cervical cancer incidence.

Citing a large body of data on screening effectiveness, the American College of Obstetrics and Gynecology recently updated their guidelines for cervical cancer screening. The guidelines are as follows : screening is recommended every 2 years to begin at age 21 years; screening should be avoided before this age because screening at younger ages may lead to unnecessary and harmful evaluation and treatment in women at very low risk of cancer. After age 30 years, the screening interval can be extended to 3 years for women who have no history of CIN 2 or CIN 3, who are not HIV-infected or otherwise immunocompromised, and who were not exposed to diethylstilbestrol (DES) in utero. Women who have had a total hysterectomy for benign conditions and who have no history of high-grade CIN may discontinue routine screening. It is also reasonable to discontinue screening for women older than 65 to 70 years who have three or more consecutive negative studies and have had no abnormal test results in the past 10 years.

Women previously treated for high-grade CIN or for cancer should continue to have annual screening for at least 20 years and periodic screening indefinitely. Annual gynecologic examination might still be appropriate even if cytologic screening is not performed.

Accurate calculation of false-negative rates for the Pap test is difficult; estimates range from less than 5% to 20% or more. The sensitivity of individual tests may be improved by ensuring adequate sampling of the squamocolumnar j unction and the endocervical canal; smears without endocervical or metaplastic cells are inadequate, and in such cases the test must be repeated.

The sensitivity of a screening program is increased by repeated testing; studies of the test frequency required to optimize the sensitivity of screening formed the basis of the American College of Obstetrics and Gynecology recommendations. Most United States gynecologists currently prefer newer liquid-based screening methods to conventional Pap tests. However, the authors of a recent meta-analysis of available data concluded that "liquid-based cervical cytology is neither more sensitive nor more specific for detection of high-grade CIN compared with the conventional Pap. Liquid-based tests are more costly but have the potential advantage that additional studies, such as HPV typing, can be performed on the fluid remaining after cytologic examination. HPV testing of ASC-US smears followed by colposcopy in patients with HPV-positive lesions has been shown to be a highly accurate and cost-effective means of detecting HSIL in cases of equivocal smears and may also be used to triage postmenopausal women with LSIL.

Patients with abnormal findings on cytologic examination who do not have a gross cervical lesion must be evaluated with colposcopy and directed biopsies.

Following application of a 3% acetic-acid solution, the cervix is examined under 10- to 15-fold magnification with a bright, filtered light that enhances the acetowhitening and vascular patterns characteristic of dysplasia or carcinoma. The skilled colposcopist can accurately distinguish between low- and high-grade dysplasia, but microinvasive disease cannot consistently be distinguished from intraepithelial lesions on colposcopy. In patients with a high-grade Pap smear finding, if no abnormalities are found on colposcopic examination or if the entire squamocolumnar junction cannot be visualized, an additional endocervical sample should be collected. Although some authorities advocate the routine addition of endocervical curettage to colposcopic examination, it is probably reasonable to omit this step i n previously untreated women if the entire squamocolumnar junction is visible with a complete ring of unaltered columnar epithelium in the lower canal. The rate of detection of endocervical lesions may be higher when specimens are collected using a cytobrush rather than by curettage. Cervical cone biopsy is used to diagnose occult endocervical lesions and is an essential step in the diagnosis and management of microinvasive carcinoma of the cervix. Cervical cone biopsy yields an accurate diagnosis and decreases the incidence of inappropriate therapy when (1) the squamocolumnar junction is poorly visualized on colposcopy and a high-grade lesion is suspected, (2) high-grade dysplastic epithelium extends into the endocervical canal, (3) the cytologic findings suggest highgrade dysplasia or carcinoma in situ, (4) a microinvasive carcinoma is found on directed biopsy, (5) the endocervical curettage specimens show high-grade CIN, or (6) the cytologic findings are suggestive of adenocarcinoma in situ.

8.6. TNM-CLASSIFICATION

Endometrial carcinoma is surgically staged using the FIGO cancer staging system. Following are presented two stage systems in comparing.

T – Primary Tumour

TNM Categories	FIGO Stages	
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis	[1]	Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumour confined to the cervix (extension to corpus should be disregarded)
T1a[2]	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less[3]
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread

T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less

Note: The depth of invasion should be taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial papillae to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.

T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumour without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumour with parametrial invasion
T3	III	Tumour extends to pelvic wall, involves lower third of vagina, causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumour involves lower third of vagina
T3b	IIIB	Tumour extends to pelvic wall, causes hydronephrosis or nonfunctioning kidney
T4	IVA	Tumour invades mucosa of the bladder or rectum, or extends beyond true pelvis[4,5]

Notes: [1]FIGO no longer includes Stage 0 (Tis). [2]All macroscopically visible lesions even with superficial invasion are T1b/IB. [3]Vascular space involvement, venous or lymphatic, does not affect classification. [4]Bullous oedema is not sufficient to classify a tumour as T4. [5]Invasion of bladder or rectal mucosa should be biopsy proven according to FIGO.

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 (includes inguinal lymph nodes and intraperitoneal disease except metastasis to pelvic serosa). It excludes metastasis to vagina, pelvic serosa, and adnexa

Stage grouping			
Stage	T	N	M
0*	Tis	N0	M0
I	T1	N0	M0
IA	T1a	N0	M0
IA1	T1a1	N0	M0
IA2	T1a2	N0	M0
IB	T1b	N0	M0
IB1	T1b1	N0	M0
IB2	T1b2	N0	M0
II	T2	N0	M0
IIA	T2a	N0	M0
IIA1	T2a1	N0	M0
IIA2	T2a2	N0	M0
IIB	T2b	N0	M0
III	T3	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	Any N	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1
FIGO більше не включає стадію 0 (Tis)			

8.7. TREATMENT

A number of factors may influence the choice of local treatment for cervical cancer, including tumor size, stage, histologic features, evidence of lymph node metastasis, risk factors for complications of surgery or radiotherapy, and patient preference. However, as a rule, HSILs are managed with a loop electroexcision procedure (LEEP); microinvasive cancers invading less than 3 mm (stage IA1) are managed with conservative surgery (excisional conization or extrafascial hysterectomy) ; early invasive cancers (stage IA2 and IB1 and some small stage IIA tumors) are managed with radical or modified radical hysterectomy, radical trachelectomy (if fertility preservation is desired), or radiotherapy; and locally advanced cancers (stages IB2 through IVA) are managed with combined chemotherapy and radiotherapy.

Selected patients with centrally recurrent disease after maximum radiotherapy may be treated with radical exenterative surgery; isolated pelvic recurrence after hysterectomy is treated with irradiation.

Preinvasive Disease

LEEP is the preferred treatment for HSIL. With this technique, a charged electrode is used to excise the entire transformation zone and distal canal. Although control rates are similar to those achieved with cryotherapy or laser ablation, LEEP is more easily learned, is less expensive than laser ablation, and preserves the excised lesion and transformation zone for histologic evaluation. LEEP is an outpatient procedure that preserves fertility. LEEP conization or excisional conization with a scalpel should be performed when microinvasive or invasive cancer is suspected and in patients with adenocarcinoma in situ. Although recurrence rates are low (1% to 5%) and progression to invasion rare (less than 1% in most series), patients treated with LEEP require careful post-LEEP surveillance.

Treatment with total hysterectomy currently is reserved for women who have other gynecologic conditions that justify the procedure; invasive cancer still must be excluded before surgery to rule out the need for a more extensive operative procedure. Microinvasive Carcinoma (Stage lA)

The standard treatment for patients with stage IA1 disease is cervical conization or total (type I) hysterectomy. Because the risk of pelvic lymph node metastases from these minimally invasive tumors is less than 1%, pelvic lymphadenectomy is not usually recommended. Patients who have FIGO stage IA1 disease without LVSI and who wish to maintain fertility may be adequately treated with a therapeutic cervical conization if the margins of the cone are negative. Although reports suggest that recurrences are infrequent, patients who have this conservative treatment must be followed very closely with periodic cytologic evaluation, colposcopy, and endocervical curettage.

The likelihood of residual invasive disease after cone biopsy is correlated with the status of the internal cone margin and the results of an endocervical curettage performed after cone biopsy. Roman et al. reported the surgical findings in 87 patients who underwent a conization that showed microinvasive squamous carcinoma, followed by either a repeat conization or hysterectomy. Residual invasive disease was present in only 4% of patients whose cone margins were free of CIN and who had no disease detected on endocervical curettage.

However, residual invasive disease was present in 13% of women who had either CIN in cone margins or positive endocervical curettage findings and 33% of women who had both of these features (P<.015), suggesting the need for a second procedure in any patient who has one of these findings.

The authors did not find any correlation between the depth of invasion or the number of invasive foci and residual invasive disease.

Therapeutic conization for microinvasive disease is usually performed with a scalpel while the patient is under general or spinal anesthesia. Because an accurate assessment of the maximum depth of invasion is critical, the entire specimen must be sectioned and carefully handled to maintain its original orientation for microscopic assessment. Complications occur in 2% to 12% of patients, are related to the depth of the cone, and include hemorrhage, sepsis, infertility, stenosis, and cervical incompetence. The width and depth of the cone should be tailored to produce the least amount of injury while providing clear surgical margins .

For patients whose tumors invade 3 to 5 mm into the stroma (FIGO stage IA2), the risk of nodal metastases is approximately 5%. Therefore, in such patients, bilateral pelvic lymphadenectomy should be performed in conjunction with modified radical (type II) hysterectomy. Modified radical hysterectomy is a less extensive procedure than classic radical (type III) hysterectomy. The uterus, cervix, upper vagina, and paracervical tissues are removed after careful dissection of the ureters to the point of their entry to the bladder.

The medial halves of the cardinal ligament and the uterosacral ligaments are also removed. With this treatment, significant urinary tract complications are rare, and cure rates exceed 95%.

Although surgical treatment is standard for in situ and microinvasive cancer, patients with severe medical problems or other contraindications to surgical treatment can be successfully treated with radiotherapy. Depending on the depth of invasion, these early lesions are treated with brachytherapy alone or brachytherapy combined with external-beam irradiation, and cure rates exceed 95%.

Stage IB and IIA Disease

Early-stage IB cervical carcinomas can be treated effectively with combined external-beam irradiation and brachytherapy or with radical hysterectomy and bilateral pelvic lymphadenectomy. The goal of both treatments is to destroy malignant cells in the cervix, paracervical tissues, and regional lymph nodes. Patients who are treated with radical hysterectomy whose tumors are found to have high-risk disease features may benefit from postoperative radiotherapy or chemoradiation.

Disease-specific survival rates for patients with stage IB cervical cancer treated with surgery or radiation usually range between 80% and 90%, suggesting that the two treatments are equally effective. However, biases introduced by patient selection, variations in the definition of stage IA disease, and variable indications for postoperative radiotherapy, concurrent chemotherapy, or adj uvant hysterectomy confound comparisons of efficacy between radiotherapy and surgery. Because young women with small, clinically node negative tumors tend to be favored candidates for surgery and because tumor diameter and nodal status are inconsistently described in published series, it is difficult to compare the results reported for patients treated with surgery and those treated with radiotherapy.

THEME 8: UTERINE, CERVICAL AND OVARIAN CANCER

Radical Trachelectomy.

In 1994, Dargent et al.l pioneered the use of radical trachelectomy and laparoscopic pelvic lymphadenectomy as a means of sparing fertility in young women with early cervical cancer.

Since then, it has been demonstrated that when these procedures are performed by experienced surgeons, the cure rates are high and many women are able to carry subsequent pregnancies to viability. Successful pregnancies have also been reported after radical abdominal trachelectomy.

In order to keep the residual uterine segment intact, a nonabsorbable cervical cerclage is placed around the uterine isthmus at the time of the trachelectomy. Alexander-Sefre et al. reported that radical trachelectomy was associated with shorter operative times and hospital stays, less blood loss, and a lower incidence of bladder hypotony than radical hysterectomy.

However, patients who had radical trachelectomy had more problems with dysmenorrhea, irregular menstruation, and vaginal discharge; in addition, 14% had cervical suture problems, 10% had isthmic stenosis, and 7% had prolonged amenorrhea. The use of radical vaginal or abdominal trachelectomy and laparoscopic lymphadenectomy may be indicated in carefully selected women with small IB1 (≤ 2 cm) lesions who are eager to preserve fertility. Patients with extensive endocervical extension are poor candidates for fertility-sparing surgery.

Preoperative MRI is a relatively sensitive and specific method to evaluate the possibility of tumor extension beyond the internal os. A recent review of 504 women who underwent radical trachelectomy summarized the outcome of 200 pregnancies. Although 84 of 200 pregnancies (42%) produced full-term viable infants, 37% of third-trimester deliveries were preterm, indicating that these women are at high risk for complicated pregnancies.

Stage IIB, III, and IVA Disease

Radiotherapy is the primary local treatment for most patients with locoregionally advanced cervical carcinoma. The success of radiotherapy depends on a careful balance between external-beam radiotherapy and brachytherapy, optimizing the dose to tumor and normal tissues and the overall duration of treatment.

For patients treated with radiotherapy alone for stage IIB, IIIB, and IV disease, 5-year survival rates of 65% to 75%, 35% to 50%, and 15% to 20%, respectively, have been reported.

Results of major clinical trials reported at the end of the 1990s indicate that, barring medical contraindications, most patients with locally advanced tumors should also receive concurrent chemotherapy along with radiotherapy. With appropriate chemoradiotherapy, even patients with massive locoregional disease have a significant chance for cure.

External-beam irradiation is used to deliver a homogeneous dose to the primary cervical tumor and to potential sites of regional spread and may also improve the efficacy of subsequent intracavitary brachytherapy by shrinking bulky tumor and bringing it within the range of the high-dose portion of the brachytherapy dose distribution. To facilitate brachytherapy, patients with locally advanced disease usually begin with a course of external-beam treatment with concurrent chemotherapy.

Subsequent brachytherapy exploits the inverse square law to deliver a high dose to the cervix and paracervical tissues while minimizing the dose to adj acent normal tissues.

Although intracavitary treatment may be delayed until pelvic irradiation has caused some initial tumor regression, breaks during or between external-beam and intracavitary therapy should be discouraged, and every effort should be made to complete the entire radiation treatment in less than 7 to 8 weeks. Several studies have suggested that treatment courses longer than 8 weeks are associated with decreased pelvic disease control and survival rates.

External-Beam Radiotherapy Technique. High-energy photons (15 to 18 MV) are usually preferred for pelvic treatment because they spare superficial tissues that are unlikely to be involved with tumor. At these energies, the pelvis can be treated either with four fields (anterior, posterior, and lateral fields) or with anterior and posterior fields alone.

When high-energy beams are not available, four fields are usually used because less-penetrating 4- to 6-m V photons often deliver an unacceptably high dose to superficial tissues when only two fields are used.

CT simulation is recommended to confirm adequate coverage of the iliac lymph nodes . Information gained from radiologic studies such as MRI, CT, and positron emission tomography can improve estimates of disease extent and assist in localization of regional nodes and paracervical tissues that may contain microscopic disease. The caudad extent of disease can be determined by inserting radiopaque markers in the cervix or at the lowest extent of vaginal disease. Potential internal organ motion must be taken into account; prospective studies have revealed that the positions of the uterus and cervix can vary by as much as 4 cm from day to day.

For this reason, it is usually wise to cover the entire presacrococcygeal region when locally advanced cancers are treated. Tumor response should be evaluated with periodic pelvic examinations. Some practitioners prefer to maximize the brachytherapy component of treatment and begin it as soon as the tumor has responded enough to permit a good placement of the brachytherapy applicators, delivering subsequent pelvic irradiation with a central shield. This technique may reduce the volume of normal tissue treated to a high dose but can also result in overdoses to medial structures such as the ureters or underdosage of posterior uterosacral disease.

For these reasons, many clinicians prefer to give an initial dose of 40 to 45 Gy to the whole pelvis, believing that the ability to deliver a homogeneous distribution to the entire region at risk for microscopic disease outweighs other considerations.

Externalbeam doses of more than 40 to 45 Gy to the central pelvis tend to compromise the dose deliverable to paracentral tissues and increase the risk of late complications.

A total dose (external-beam and intracavitary) of 45 to 55 Gy appears to be sufficient to sterilize microscopic disease in the pelvic nodes in most patients . It is customary to treat lymph nodes known to contain gross disease and heavily involved parametria to a total dose of 60 to 65Gy (including the contribution from brachytherapy treatments).

Intensity-Modulated Radiotherapy. There has been a recent surge of interest in possible applications of intensity-modulated radiotherapy (IMRT) and other forms of highly conformal radiotherapy in patients with gynecologic tumors. Unlike standard two-field and four-field techniques, IMRT makes it possible to deliver a lower daily dose to the intrapelvic contents than to surrounding pelvic lymph nodes. Some of the most intriguing uses of IMRT involve treatment of gross regional disease. With standard techniques, the close proximity of bowel has made it difficult to sterilize disease in nodes larger than 2 cm; IMRT allows delivery of doses exceeding 60Gy to regional nodes with relative sparing of adjacent critical structures.

However, the highly conformal dose distributions achievable with IMRT also increase the potential for error and require considerable experience and attention to detail on the part of the radiation oncologist. In particular, great attention must be paid to the influence of internal organ motion and intratreatment tumor response on the doses to tumor and critical structures. Although some investigators have begun to explore the use of IMRT to treat patients with intact cervical cancers, large interand intratreatment variations in the position and size of the target volume raise serious concerns about the risk of missing tumor with these highly conforming treatments; if very ample margins are used to account for variability in the target, the gain relative to simpler treatments may not j ustify such complex treatment.

There is no evidence that IMRT can safely be used as an alternative to brachytherapy for routine treatment of intact cervical cancer. Although IMRT achieves very conformal dose distributions, it cannot accurately reproduce the high-dose gradients produced with intracavitary brachytherapy.

More importantly, the large, unpredictable variations that occur in the positions of the bladder, rectum, and target mandate the use of large treatment margins that inevitably encompass adjacent critical structures and reduce the dose deliverable to tumor.

Stage IVB Disease

Patients who present with disease in distant organs are almost always incurable. The care of these patients must emphasize palliation of symptoms with use of appropriate pain medications and localized radiotherapy. Tumors may respond to chemotherapy, but responses are usually brief.

Single-Agent Chemotherapy. Cisplatin has been studied in a variety of doses and schedules in the management of recurrent or metastatic cervical cancer and is considered the most active agent against this malignancy. Although a number of other agents (e.g., ifosfamide, carboplatin, irinotecan, and paclitaxel) have exhibited a modest level of biologic activity in cervical cancer (producing response rates of 10% to 15%), the clinical utility of these drugs in patients who have not responded to cisplatin or who have experienced recurrence or progression after chemoradiation is uncertain. Further, it is well recognized that the objective rate of response to chemotherapy is lower in previously irradiated areas (e.g., pelvis) than in nonirradiated sites (e.g., lung).

Combination Chemotherapy. Most reports of combination chemotherapy for carcinoma of the cervix have described small, uncontrolled phase 2 trials of drug combinations.

The results of two phase 3 randomized trials, published in 2004 and 2005, have provided the first solid evidence that combination chemotherapy can improve both progression-free survival (cisplatin plus paclitaxel vs. single-agent cisplatin, cisplatin plus topotecan vs. single-agent cisplatin) and overall survival (cisplatin plus topotecan vs. single-agent cisplatin) when it is administered for recurrent or metastatic carcinoma of the cervix. However, a recently reported phase 3 trial comparing combinations of cisplatin with either topotecan, paclitaxel, gemcitabine, or vinorelbine revealed no significant differences in outcome between patients treated with the four cisplatin-based regimens.

Palliative Radiotherapy. Localized radiotherapy can provide effective relief of pain caused by metastases in bone, brain, lymph nodes, or other sites. A rapid course of pelvic radiotherapy can also provide excellent relief of pain and bleeding for patients who present with incurable disseminated disease.

8.8. QUESTIONS FOR SELF-CONTROL
1. What place does cervical cancer take in the structure of oncological diseases? Give a characteristic of it.
2. What is the incidence of cervical cancer in the industrial counries?
3. At what age is the cancer of the cervix diagnosed more frequently?
4. Name two main morphological forms of lung cancer.
5. What is the pathogenesis of cervical cancer?
6. Give a characteristic of the early stage cancer of the cervix.
7. Give a characteristic of the locally spread cancer of the cervix.
8. What method of treatment is the main at the cancer of the cervix?

9. How does cervical cancer spread?
10. What is the main colposcopy signs of cervical cancer?

8.9. TESTS FOR SELF-CONTROL

1. Most typical histologic type of cervical cancer:
   a. Adenocarcinoma
   b. Myoma
   c. Squamous cell carcinoma
   d. Mesonephroid cancer
2. The leading colposcopy sign of cervical cancer:
   a. Lesion color
   b. Lesion borders
   c. Capillary structure
   d. Lesion surface
3. The most important method for detecting precancer cervical lesions?
   a. Cytological examination
   b. Cervical biopsy
   c. MRI
   d. Colposcopy
4. What sign determinates the indication for organ-saving operation:
   a. Age of the woman
   b. Stage of disease
   c. Wish of the patient
   d. Anatomical status of the cervix
5. What are common method of material collection for cytological examination of the endometrium:
   a. Aspiration
   b. Contact
   c. Puncture
   d. Biopsy

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

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THEME 9

KIDNEY, URETHRAL AND BLADDER CANCER

KIDNEY CANCER

9.1. EPIDEMIOLOGY

Each year in the United States there are approximately 57,000 cases of kidney and upper urinary tract cancer, resulting in more than 12,900 deaths. These tumors account for approximately 3% of adult malignancies and occur in a male-female ratio of 1.6:1. They are more common among urban than rural residents.

Although most cases of renal carcinoma occur in persons aged 50 to 70 years, it has been observed in children as young as 6 months of age. Between 1975 and 1995 there was a steady and significant increase in the incidence of renal carcinoma, from 2% to 4% per year, an increase of 43% since 1973.

Renal carcinoma was first described by Konig in 1826. As early as 1855 Robin concluded that the renal tubular epithelium was the most probable tissue of origin of the cancer, an observation that was confirmed by Waldeyer in 1867. In 1883 Grawitz, noting that the fatty content o f the cancer cells was similar to that of adrenal cells, concluded that the tumors arose from adrenal rests within the kidney and introduced the term stroma lipomatodes aberrata renis for these clear cell tumors. The term hypernephroid tumors was introduced in 1984 by Birch-Hirschfeld. Since then the conceptually incorrect term hypernephroma has frequently been applied to renal tumors

9.2. ETIOLOGY

A number of environmental, hormonal, cellular, and genetic factors have been studied as possible causal factors in the development of renal carcinoma. In studies of risk of renal adenocarcinoma, cigarette smoking has been found to be a risk factor. A statistically significant dose response has been observed in both genders for pack-years of cigarette use. It has been estimated that 30% of renal carcinomas in men and 24% in women may be directly related to smoking. Obesity is associated with an increased risk of development of renal carcinoma, particularly in women and particularly in patients with clear cell kidney cancer. Analgesic abuse, which is known to be associated with renal pelvis cancer, is also associated with an increased incidence of kidney cancer. The increased risk for the development of renal carcinoma is observed primarily in patients who develop analgesic nephropathy associated with use of phenacetin-containing analgesics. Environmental and occupational factors have also been associated with the development of kidney cancer. Brauch et al. demonstrated an association between the development of renal carcinoma and long-term exposure to high levels of the industrial solvent, trichloroethylene (TRI). There is an increased incidence of renal carcinoma among leather tanners, shoe workers, and workers exposed to asbestos. Exposure to cadmium is associated with an increased incidence of kidney cancer, particularly in men who smoke.

An association between gasoline fume exposure and kidney cancer has been observed in animal studies. Although there is an increased incidence of renal carcinoma reported with exposure to petroleum, tar, and pitch products, studies of oil refinery workers and petroleum products distribution workers do not identify a definite relationship between gasoline exposure and renal cancer.

There may be an increase risk of kidney cancer in older workers or in workers exposed to gasoline for prolonged periods of time. There is an increased incidence (100-fold) of renal carcinoma in patients with end-stage renal disease who develop acquired cystic disease of the kidneys. Acquired cystic disease is a recently described phenomenon in which patients on long-term dialysis for renal failure develop renal cysts. Renal carcinoma has been found in association with the papillary hyperplasia observed in the cyst epithelium of these kidneys .

The risk of developing kidney cancer has been estimated to be greater than 30 times higher in dialysis patients with cystic changes in their kidney than in the general population. It is estimated that 35% t o 47% o f patients o n long-term dialysis will develop acquired cystic disease, and that about 5.8 % of the patients with acquired cystic disease will develop renal cancer. Kidney cancer can develop at any time in patients with end-stage renal disease, and it can occur in kidney transplant recipients. Kidney cancer can occur in patients with end-stage renal disease who are undergoing either hemodialysis or chronic ambulatory dialysis, and it has been reported to occur in patients with end-stage renal disease who are not being dialyzed. Although many of these cancers are clinically insignificant and are found incidentally at autopsy or after bilateral nephrectomy, some will have an aggressive course. Careful surveillance of patients with end-stage
renal disease with ultrasonography and computed tomography is recommended. Family history is also associated with an increased risk of kidney cancer in both men and women.

9.3. HISTOLOGIC TYPES OF RENAL CARCINOMA

Kidney cancer is not a single disease; it is made up of a number of different types of cancer that occur in the kidney, including clear cell (75%), type 1 and type 2 papillary (15%), chromophobe (5%), and oncocytoma (5%). These cancers have different histologic types and different clinical courses, and they are caused by different genetic abnormalities.

Types

In addition to renal cell carcinoma and renal pelvis carcinoma, other, less common types of kidney cancer include:

- Squamous cell carcinoma
- Juxtaglomerular cell tumor (reninoma)
- Angiomyolipoma
- Renal oncocytoma

- Bellini duct carcinoma
- Clear-cell sarcoma of the kidney
- Mesoblastic nephroma
- Wilms' tumor, usually is reported in children under the age of 5.
- Mixed epithelial stromal tumor

Rarely, some other types of cancer and potentially cancerous tumors that more usually originate elsewhere can originate in the kidneys. These include:

- Clear cell adenocarcinoma
- Transitional cell carcinoma
- Inverted papilloma
- Renal lymphoma
- Teratoma
- Carcinosarcoma
- Carcinoid tumor of the renal pelvis

Cancer in the kidney may also be secondary, the result of metastasis from a primary cancer elsewhere in the body.

9.4. CLINICAL PRESENTATION

The most common signs and symptoms of kidney cancer are a lump in the abdomen and/or blood in the urine (or hematuria). Other symptoms may include tiredness, loss of appetite, weight loss, a high temperature and heavy sweating, and persistent pain in the abdomen. However many of these symptoms can be caused by other conditions, and there may also be no signs or symptoms in a person with kidney cancer, especially in the early stages of the disease.

9.5. TNM-CLASSIFICATION

T – Primary Tumour

TX   Primary tumour cannot be assessed

T0   No evidence of primary tumour

T1   Tumour 7 cm or less in greatest dimension, limited to the kidney

T1a   Tumour 4 cm or less

T1b   Tumour more than 4 cm but not more than 7 cm

T2   Tumour more than 7 cm in greatest dimension, limited to the kidney

T2a   Tumour more than 7 cm but not more than 10 cm

T2b   Tumour more than 10 cm, limited to the kidney

T3   Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia

T3a   Tumour grossly extends into the renal vein or its segmental (muscle containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic) fat but not beyond Gerota fascia

T3b   Tumour grossly extends into vena cava below diaphragm

T3c   Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava

T4   Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)

N – Regional Lymph Nodes

NX   Regional lymph nodes cannot be assessed

N0   No regional lymph node metastasis

N1   Metastasis in a single regional lymph node

N2   Metastasis in more than one regional lymph node

M – Distant Metastasis

M0   No distant metastasis

M1   Distant metastasis

Stage grouping

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IV	T4	Any N	M0
	Any T	N2	M0
	Any T	Any N	M1

9.6. TREATMENT

LOCALIZED RENAL CARCINOMA
Surgical Treatment

Surgery is the only known effective therapy for localized renal carcinoma. The first nephrectomy was performed by Eratus B. Walcott in Milwaukee, Wisconsin, on June 4, 1861, on a 58-year-old man with a kidney tumor who died 15 days after surgery. Professor Gustave Simon, after completing a number of experimental nephrectomies on dogs, undertook the first deliberate, planned, and successful nephrectomy in Heidelberg on August 2, 1889, in a patient with a persistent ureteral fistula.

The first successful nephrectomy in a patient with kidney cancer was performed in 1883 by Grawitz. Since that first nephrectomy, there have been significant advances in surgical techniques involving the introduction of the thoracoabdominal approach to laparoscopic radical nephrectomy and changes in the surgical approach, including the use of laparoscopic and robotic partial nephrectomy for small renal tumors .

The most common procedure today for treatment of localized renal carcinoma greater than 4 em is radical nephrectomy. Radical nephrectomy includes complete removal of Gerota's fascia and its contents, including the kidney and the adrenal gland, and provides a better surgical margin than simple removal of the kidney. However, in the 1990s a series of articles reported that partial nephrectomy resulted in better functional and equal oncologic outcome. As surgical techniques have improved, many are advocating partial nephrectomy even in patients with 4- to 7-cm tumors. Radical nephrectomy is associated with significant adverse effects compared with partial nephrectomy, and partial nephrectomy should be considered for most patients with small renal tumors.

Laparoscopic nephrectomy has become the preferred method for removal of kidney tumors. As advances with this technique are growing, this approach has become the standard of care for management of most renal tumors not amenable to nephron-sparing surgery. The technique is associated with cancer control equivalent to open radical nephrectomy and is associated with decreased hospital stay, more rapid convalescence, decreased postoperative pain, and improved cosmesis.

Laparoscopic nephrectomy is most often used as a means of performing minimally invasive cytoreductive nephrectomy in patients with advanced RCC as preparation for immunologic therapy.

In patients with locally advanced RCC (N+), there is currently no evidence to date that neoadj uvant or adj uvant surgical treatment of patients with agents such as sunitinib increases survival. In patients in whom all visible disease has been resected surgically, most physicians recommend treatment when residual or recurrent disease becomes detectable. It is not known whether agents such as sunitinib (in either the neoadjuvant or adjuvant setting) will decrease recurrence rates or increase survival.

<u>Bilateral Renal Carcinoma, Tumors in Solitary Kidneys, and Renal Tumors</u>

The treatment of patients with either bilateral renal carcinoma or renal carcinoma in a solitary kidney is evolving toward a more minimally invasive approach. Patients with tumor in a solitary kidney may be treated by either partial nephrectomy or nephrectomy followed by dialysis or transplantation if the tumor is too large for a partial nephrectomy. Nephron-sparing surgery may be recommended for patients with sporadic renal cell cancer, particularly those with a small tumor (7 cm or less) or a tumor in a solitary kidney. Nephron-sparing surgery for localized renal tumors has been found to be a safe procedure, providing long-term tumor control and preservation of renal function.

Laparoscopic and robotic partial nephrectomy provides a minimally invasive alternative for carefully selected patients with renal carcinoma. This technique has been shown to be a viable alternative for selected patients with renal tumors and is associated with excellent tumor control and preservation of renal function.

Other approaches for minimally invasive nephron-sparing therapy of renal carcinoma, such as cryotherapy and radiofrequency ablation, are currently being evaluated. These techniques provide promise for the further development of effective forms of therapy with significant decrease in morbidity.

Currently these approaches are most appropriate for elderly patients or those who have significant comorbidities who would not be candidates for surgical intervention.

Surgical Management of Patients with Hereditary Forms of Renal Carcinoma

Patients with hereditary forms of renal carcinoma are often challenging to manage. Individuals with VHL, HPRC, or BHD can have widespread renal involvement. Surgical management in these patients involves careful parenchymal sparing surgery, which is recommended when the renal tumors reach a certain size threshold, generally 3 cm. The use of parenchymal sparing surgery in these patients is based on a strategy designed to maintain the patient's renal function as long as possible while decreasing the risk for metastasis. Patients who are affected with HLRCC are at risk for the development of an aggressive form of type 2 papillary renal carcinoma that can metastasize early. In these patients early surgical intervention is recommended.

Management of Small, Incidentally Detected Renal Masses

The experience with expectant management of small renal tumors in VHL, HPRC, and BHD patients has raised the question whether it might be appropriate to manage conservatively small incidentally detected renal masses in the nonhereditary patient population. A number of studies suggest that active surveillance of patients with renal tumors less than 4 cm may be appropriate for selected patients who are elderly or unsuited for surgery. However, for patients who are surgical candidates, most experienced clinicians recommend surgical therapy. It is currently not possible to determine by preoperative imaging studies which small renal tumors will grow slowly and which will metastasize early. Tumors such as type 2 papillary renal carcinoma, collecting duct carcinoma, and medullary renal carcinoma are particularly aggressive and may spread from even a
small-size renal tumor.

METASTATIC RENAL CARCINOMA
Cytoreductive Nephrectomy for Palliation

Adjuvant or palliative nephrectomy is not infrequently performed in patients with zetastatic renal carcinoma, particularly those with pain, hemorrhage, malaise, hypercalcemia, erythrocytosis, or hypertension. Removal of the primary tumor may alleviate some or all of these abnormalities. Although there are isolated reports of regression of metastatic renal carcinoma following removal of the primary tumor, only 4 of 474 (0.8%) patients in nine series who underwent nephrectomy experienced "regression" of metastatic foci.

Cytoreductive Nephrectomy in the Management of Metastatic Renal Carcinoma

DeKernion et aJ. reported results in 26 patients with metastatic renal carcinoma who underwent palliative nephrectomy and found no increase in survival, compared with survival in the entire group of 79 patients with metastatic renal carcinoma. In the context of metastatic disease, nephrectomy alone has not been associated with a survival benefit.

Nephrectomy is not recommended for the purpose of inducing spontaneous regression; rather, it is performed to control symptoms or to decrease tumor burden in association with subsequent therapy.

Two large randomized trials have been performed to address the role of nephrectomy followed by interferon alfa-based immunotherapy compared with interferon alfa alone in metastatic RCC. Flanigan et aJ. found the median survival of 120 patients assigned to surgery followed by interferon alfa to be 11.1 months compared to 8.1 months in 121 patients assigned to interferon alfa alone (P =.05). Mickisch et aJ. found time to progression (5 months vs. 3 months) and median duration of survival to be better in patients randomized to surgery plus interferon alfa patients compared to those randomized to interferon alfa alone. Although there are no data to indicate that nephrectomy alone improves survival, these studies indicate that in well-selected patients with good performance status, nephrectomy plus interferon results in improved outcome among patients with metastatic renal carcinoma as opposed to interferon alone.

Nephrectomy in patients with advanced RCC should be considered in the context of a treatment plan that includes systemic therapy. The use of laparoscopic nephrectomy in patients with advanced disease provides a potentially less-invasive method for cytoreduction as preparation for administration of systemic therapies. Studies are currently in progress to evaluate the role of targeted therapy and nephrectomy in patients with advanced kidney cancer.

Resection of Metastases

Of the approximately 30% of patients with renal carcinoma who present with metastases, only 1.5% to 3.5% have a solitary metastasis.

Patients with a solitary metastasis synchronous with a primary lesion have decreased survival when compared with patients who develop metastasis after the primary tumor is removed. Surgical resection is appropriate in selected patients with metastatic renal carcinoma. In one study, patients with renal carcinoma who underwent surgical resection for a solitary metastasis had a 45% 3-year survival and a 34% 5-year survival. O'Dea et al. reported on patients who presented with primary tumor in place and a solitary metastasis.

Of the patients who underwent nephrectomy and who later developed metastasis, 23% lived more than 5 years after removal of the metastatic lesions. Three of the 26 patients were alive 58, 94, and 245 months after resection of the metastatic lesions. In a report by van der Poel et al., better survival was found for lung metastases when compared with other sites of metastasis. In this study, 1 4 % were free of disease at 45 months, while long-term (greater than 5 years) disease-free survival was observed in 7%. Resection of metastases will render few cures but will frequently produce some long-term survivors.

Debulking Nephrectomy

Debulking nephrectomy has become a standard of care in selected metastatic RCC patients on the basis of two prospective trials that randomized metastatic RCC patients to radical nephrectomy or no surgery, followed by interferon alfa for all patients. A combined analysis of these trials demonstrated an overall survival advantage for the nephrectomy group (13.6 months survival with debulking nephrectomy versus 7.8 months for the interferon alone arm) despite no difference in objective response rate. The mechanism of survival benefit related to debulking nephrectomy, however, remains obscure. Appropriate candidates for debulking nephrectomy include patients with (1) good performance status; (2) a resectable primary tumor that represents the maj ority of total tumor burden; (3) no evidence of rapidly progressing extrarenal disease; and (4) no prohibitive medical comorbidities. It is noteworthy that the selection criteria noted above are largely subjective, based on patients treated in the cytokine era, and very few prospective data with obj ective parameters exist.

Delayed nephrectomy after systemic therapy is also a reasonable strategy, allowing assessment of response to systemic therapy and overall disease pace, thus allowing more appropriate patient selection for surgery and potential down-staging of the primary tumor. This latter strategy may be more relevant in the modern era with agents that have more overall antitumor effect and can have that effect in the primary tumor. The lack of insight into the biologic alterations of nephrectomy precludes definitive statements about the relative timing of debulking nephrectomy. Prospective clinical trials are planned to investigate this issue and will randomize metastatic RCC patients to upfront nephrectomy or not followed by sunitinib.

THEME 9: KIDNEY, URETHRAL AND BLADDER CANCER

Surgical Resection of Metastatic Disease

The biology of RCC is unique and variable, including a small subset of patients who present with low-volume, radiographically solitary or limited metastases. These metastases may be present at the time of initial presentation or have been present many months to years after initial nephrectomy. Such patients with limited metastatic disease may be considered for surgery to remove all visible disease. This approach can yield a 30% 5-year disease-free survival.

Characteristics that predict a more favorable outcome include a long interval between initial diagnosis and development of metastases, which reflects an indolent course and reinforces the likelihood that the metastasis is truly solitary, and the ability for complete resection (e.g., solitary lung metastasis). Therefore, surgical resection of metastases can be considered in highly select RCC patients. However, whether metastasectomy is truly altering the natural history or extending survival of such patients, who by definition have low-volume, slow-growing disease, can be debated.

Angioinfarction

Angioinfarction refers to embolization of the renal artery in an attempt to reduce renal blood flow to the tumor. This procedure has historically been performed for symptomatic control of a primary tumor (e.g., bleeding control) if surgical intervention was not possible or was delayed. Refinements in surgical technique have made nephrectomy possible for the vast maj ority of patients. This, coupled with a decrease in symptomatic primary tumors due to earlier detection from widespread imaging (and thus reduced tumor size), has lessened the use of angioinfarction. It is an accepted current practice for palliation or if renal vessels are encased by tumor to facilitate subsequent surgery. In patients with metastatic disease, angioinfarction was attempted early as a replacement for debulking nephrectomy or in an attempt to induce antigen release to make subsequent immunotherapy more effective. Although no prospective, randomized data exist, no definitive benefit of this approach was realized. Angioinfarction thus does not impact subsequent systemic therapy and should be undertaken only for palliative or surgical indications.

Chemotherapy

Based on the success in other solid tumors, chemotherapy for advanced RCC has been extensively studied. A summary of clinical trials from 1983 to 1993 noted a 6% overall response rate in 4,093 patients with advanced RCC. Another report of 51 published phase 2 clinical trials (n = 1 ,347) involving 3 3 chemotherapeutic agents noted an overall response rate o f 5.5%. No single chemotherapeutic agent has reproducibly demonstrated response rates more than 10%. Combinations of 5-fluorouracil and analogues with gemcitabine have produced modestly higher response rates on the order of 10% to 15%.

Similarly, the addition of chemotherapy to cytokine regimens has not resulted in significant benefit over cytokine alones when investigated in phase 3 trials.

A report of 18 metastatic RCC patients with sarcomatoid histologic features or rapidly progressing disease treated with doxorubicin and gemcitabine noted a 28% objective response rate, potentially identifying a subset o f RCC patients where chemotherapy may have some utility. Overall, chemotherapy currently has little to no role in the treatment of metastatic RCC pending further study of novel chemotherapeutic agents or combinations, or perhaps through additional patient selection efforts.

The mechanisms of chemotherapy resistance postulated in RCC include reduced drug accumulation due to the expression of transport proteins such as P-glycoprotein, increased detoxification, altered targets, and impaired apoptosis pathways. The best described is P-glycoprotein, a 170-kD membrane glycoprotein expressed on RCC cells that can act as an efflux pump, reducing intracellular concentrations of agents such as vinblastine.

In view of this, compounds inhibiting P-glycoprotein such as toremifene, verapamil, nifedipine, and cyclosporin in combination with vinblastine have been investigated. To date, these combinations have not improved response rates, and it is likely that additional mechanisms are responsible for the resistance to chemotherapeutic agents in renal cancer patients.

Hormonal Therapy

The limited available data that would suggest the presence of steroid receptors in renal carcinoma tumors are rare. A single animal model demonstrated that a progestational agent inhibited the growth of diethylstilbestrol-induced renal tumors in Syrian hamsters. Despite this, the historic lack of other effective agents in RCC lead to the use of hormonal agents, mostly progestational agents such as medroxyprogesterone acetate (MPA), in metastatic RCC in the 1970s and 1980s.

These early reports documented some tumor regression and symptom reduction, largely applied to a very advanced, symptomatic population of RCC patients. These studies failed to correlate antitumor effect with the level of steroid receptor resent within tumor tissue, and thus the mechanism of any effect is largely unproven. More recent multicenter randomized trials utilized oral MPA as an initial therapy for patients with metastatic renal cancer in comparison to cytokines. Response rates to MPA were uniformly low (2.0% and 2.5%, respectively). In the current era of active drugs in RCC, progestational agents may be useful for symptom palliation, but they do not appear to have any significant antitumor effects.

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<u>Vascular Endothelial Growth Factor-Targeted Therapy</u>

RCC presents a unique clinical setting for the application of antiangiogenic approaches. Through mutations in the VHL gene or other genetic events that result in the dysregulated expression of the hypoxia-inducible transcription factors (HIF-1 a and HIF-2(3), a large cohort of hypoxia-responsive genes is induced, including vascular endothelial growth factor (VEGF) as one of the classic transcriptional targets. Cell culture model systems of RCC have demonstrated a direct link between VHL mutation and up-regulation of angiogenesispromoting proteins including VEGF and platelet-derived growth factor (PDGF). Thus, increased expression of these proteins, and the consequences of that increased expression, is central in the development of most RCC tumors. VEGF is the major factor responsible for tumor angiogenesis, and PDGF is a critical signaling protein for pericytes, which serve as structural supporting cells for blood vessels. Several treatment strategies have thus been investigated in metastatic RCC to block components of the angiogenic signaling pathway components such as VEGF and PDGF.

BLADDER CANCER

9.7. EPIDEMIOLOGY

In the United States, bladder cancer is the fourth most common type of cancer in men and the ninth most common cancer in women. More than 50,000 men and 16,000 women are diagnosed with bladder cancer each year. Smoking can only partially explain this higher incidence in men. One other reason is that the androgen receptor, which is much more active in men than in women, plays a major part in the development of the cancer.

Bladder cancer is any of several types of malignancy arising from the epithelial lining (i.e., the urothelium) of the urinary bladder. Rarely the bladder is involved by non-epithelial cancers, such as lymphoma or sarcoma, but these are not ordinarily included in the colloquial term "bladder cancer." It is a disease in which abnormal cells multiply without control in the bladder. The bladder is a hollow, muscular organ that stores urine; it is located in the pelvis. The most common type of bladder cancer recapitulates the normal histology of the urothelium and is known as transitional cell carcinoma. It is estimated that there are 383,000 Bladder cancer cases worldwide.

9.8. ETIOLOGY

Tobacco smoking is the main known contributor to urinary bladder cancer; in most populations, smoking is associated with over half of bladder cancer cases in men and one-third of cases among women. There is a linear relationship between smoking and risk, and quitting smoking reduces the risk.

Passive smoking has not been proven to be involved. In a 10-year study involving almost 48,000 men, researchers found that men who drank 1.5L of water a day had a significantly reduced incidence of bladder cancer when compared with men who drank less than 240mL (around 1 cup) per day. The authors proposed that bladder cancer might partly be caused by the bladder directly contacting carcinogens that are excreted in urine, although this has not yet been confirmed in other studies. Thirty percent of bladder tumors probably result from occupational exposure in the workplace to carcinogens such as benzidine. 2-Naphthylamine, which is found in cigarette smoke, has also been shown to increase bladder cancer risk. Occupations at risk are bus drivers, rubber workers, motor mechanics, leather (including shoe) workers, blacksmiths, machine setters, and mechanics. Hairdressers are thought to be at risk as well because of their frequent exposure to permanent hair dyes. A 2008 study commissioned by the World Health Organisation concluded that "specific fruit and vegetables may act to reduce the risk of bladder cancer." Fruit and yellow-orange vegetables, particularly carrots and those containing selenium, are probably associated with a moderately reduced risk of bladder cancer. Citrus fruits and cruciferous vegetables were also identified as having a possibly protective effect.

It has been suggested that mutations at HRAS, KRAS2, RB1, and FGFR3 may be associated in some cases

9.9. PATHOLOGY

90% of bladder cancers are transitional cell carcinoma. The other 10% are squamous cell carcinoma, adenocarcinoma, sarcoma, small cell carcinoma, and secondary deposits from cancers elsewhere in the body.[citation needed]

Carcinoma in situ (CIS) invariably consists of cytologically high grade tumour cells.

9.10. CLINICAL FEATURES

Bladder cancer characteristically causes blood in the urine; this may be visible to the naked eye (gross hematuria) or detectable only by microscope (microscopic hematuria).

Other possible symptoms include pain during urination, frequent urination (polyuria), or feeling the need to urinate without results. These signs and symptoms are not specific to bladder cancer, and are also caused by non-cancerous conditions, including prostate infections and cystitis. Kidney cancer also can cause hematuria.

9.11. DIAGNOSTICS

Bladder tumor in FDG PET due to the high physiological FDG-concentration in the bladder, furosemide was supplied together with 200 MBq FDG. The uptake cranial to the lesion is a physiological uptake in the colon.

Many patients with a history, signs, and symptoms suspicious for bladder cancer are referred to a urologist or other physician trained in cystoscopy, a procedure in which a flexible tube bearing a camera and various instruments is introduced into the bladder through the urethra. Suspicious lesions may be biopsied and sent for pathologic analysis.

The gold standard for diagnosing bladder cancer is biopsy obtained during cystoscopy. Sometimes it is an incidental finding during cystoscopy. Urine cytology can be obtained in voided urine or at the time of the cystoscopy ("bladder washing"). Cytology is very specific (a positive result is highly indicative of bladder cancer) but suffers from low sensitivity (inability of a negative result to reliably exclude bladder cancer). There are newer non-invasive urine bound markers available as aids in the diagnosis of bladder cancer, including human complement factor H-related protein, high-molecular-weight carcinoembryonic antigen, and nuclear matrix protein 22 (NMP22). NMP22 is also available as a prescription home test. Other non-invasive urine based tests include the CertNDx Bladder Cancer Assay, which combines FGFR3 mutation detection with protein and DNA methylation markers to detect cancers across stage and grade, and the UroVysion test.

The diagnosing of bladder cancer can also be done with a Cysview guided fluorescence cystoscopy (blue light cystoscopy, Photodynamic diagnosis), as an adjunct to conventional white-light cystoscopy. This procedure improves the detection of bladder cancer and reduces the rate of early tumour recurrence, compared with white-light cystoscopy alone. Cysview cystoscopy detects more cancer and reduce recurrency. Cysview is marketed in Europe under the brand name Hexvix.

However, visual detection in any form listed above, is not sufficient for establishing pathological classification, cell type or the stage of the present tumor. A so called cold cup biopsy during an ordinary cystoscopy (rigid or flexible) will not be sufficient for pathological staging either. Hence, a visual detection needs to be followed by transurethral surgery. The procedure is called transurethral resection TUR. Further, bimanual examination should be carried out before and after the TUR to assess whether there is a palpable mass or if the tumour is fixed ("tethered") to the pelvic wall. The pathological classification obtained by the TUR-procedure, is of fundamental importance for making the appropriate choice of ensuing treatment and/or follow-up routines.

9.12. TNM-CLASSIFICATION

T – Primary Tumour

The suffix (m) should be added to the appropriate T category to indicate multiple tumours. The suffix (is) may be added to any T to indicate presence of associated carcinoma in situ.

TX   Primary tumour cannot be assessed

T0   No evidence of primary tumour

Ta   Non-invasive papillary carcinoma
Tis   Carcinoma in situ: 'flat tumour'
T1   Tumour invades subepithelial connective tissue
T2   Tumour invades muscle
T2a   Tumour invades superficial muscle (inner half)
T2b   Tumour invades deep muscle (outer half)
T3   Tumour invades perivesical tissue:
T3a   microscopically
T3b   macroscopically (extravesical mass)
T4   Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a   Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
T4b   Tumour invades pelvic wall or abdominal wall

N – Regional Lymph Nodes
NX   Regional lymph nodes cannot be assessed
N0   No regional lymph node metastasis
N1   Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2   Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3   Metastasis in a common iliac lymph node(s)

M – Distant Metastasis
M0   No distant metastasis
M1   Distant metastasis

Stage grouping

Stage	T	N	M
0a	Ta	N0	M0
0is	Tis	N0	M0
I	T1	N0	M0
II	T2a-b	N0	M0
III	T3a-b	N0	M0
	T4a	N0	M0
	T4a	N0	M0
IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

9.13. TREATMENT

The treatment of bladder cancer depends on how deep the tumor invades into the bladder wall. Superficial tumors (those not entering the muscle layer) can be "shaved off" using an electrocautery device attached to a cystoscope, which in that case is called a resectoscope. The procedure is called transurethral resection - TUR - and serves primarily for pathological staging. In case of non-muscle invasive bladder cancer the TUR is initself the treatment, but in case of muscle invasive cancer, the procedure is insufficient for final treatment.Immunotherapy in the form of BCG instillation is also used to treat and prevent the recurrence of superficial tumors.

BCG immunotherapy is effective in up to 2/3 of the cases at this stage. Instillations of chemotherapy, such as valrubicin (Valstar) into the bladder can also be used to treat BCG-refractory CIS disease when cystectomy is not an option. Urocidin is phase III trials for this.

Patients whose tumors recurred after treatment with BCG are more difficult to treat. Many physicians recommend Cystectomy for these patients. This recommendation is in accordance with the official guidelines of the European Association of Urologists (EAU) and the American Urological Association (AUA) However, many patients refuse to undergo this life changing operation, and prefer to try novel conservative treatment options before opting to this last radical resort. Device assisted chemotherapy is one such group of novel technologies used to treat superficial bladder cancer. These technologies use different mechanisms to facilitate the absorption and action of a chemotherapy drug instilled directly into the bladder. Another technology uses an electrical current to enhance drug absorption. Another technology, thermotherapy, uses radio-frequency energy to directly heat the bladder wall, which together with chemotherapy shows a synergistic effect, enhancing each other's capacity to kill tumor cells. This technology was studied by different investigators.

Untreated, superficial tumors may gradually begin to infiltrate the muscular wall of the bladder. Tumors that infiltrate the bladder require more radical surgery where part or all of the bladder is removed (a cystectomy) and the urinary stream is diverted into an isolated bowel loop (called an ileal conduit or Urostomy). In some cases, skilled surgeons can create a substitute bladder (a neobladder) from a segment of intestinal tissue, but this largely depends upon patient preference, age of patient, renal function, and the site of the disease.

A combination of radiation and chemotherapy can also be used to treat invasive disease. It has not yet been determined how the effectiveness of this form of treatment compares to that of radical ablative surgery.

Photodynamic diagnosis may improve surgical outcome on bladder cancer.

For muscleinvasive urothelial urinary bladder cancer there are a number of treatment options. Gold standard is radical cystectomy as mentioned. In males this usually includes also the removal of the prostate and in females; ovaries, uterus and parts of the vagina.

In order to address the problem of micrometastatic disease which initself has implications on longtime survival, new treatment options are dearly needed. Micrometastatic dissemination is often not treatable with only major surgery and the concept of neoadjuvant chemotherapy has evolved. In a number of meta-analyses of randomised prospective trials worldwide, the results have shown survival benefits between 5-8% with this therapy, in a follow up time of 5 years. Thus patients first receive chemotherapy in 3 or 4 cycles, and first after that proceed to major surgery.

9.14. QUESTIONS FOR SELF-CONTROL
1. What place does kidney cancer take in the structure of oncological diseases? Give a characteristic of it.
2. What is the incidence of kidney cancer in the industrial counries?
3. At what age is the kidney cancer diagnosed more frequently?
4. Name main morphological forms of bladder cancer.
5. What is the pathogenesis of bladder cancer?
6. Give a characteristic of the early stage kidney cancer.
7. Give a characteristic of the locally spread kidney cancer.
8. What method of treatment is the main at the kidney cancer?
9. How does bladder cancer spread?
10. What is the main diagnostic signs of kidney cancer?

9.15. TESTS FOR SELF-CONTROL
1. What is the common morphologic form of the kidney cancer (KC)?
    a. Squamous cell carcinoma
    b. Renall cell carcinoma
    c. Nondifferentiated
    d. adenocarcinoma
2. How often is the hematuria confirmed the kidney cancer?
    a. Always
    b. Seldom
    c. Half of causes
    d. Never
3. What is the most important sign of the bladder cancer?
    a. Dysuria
    b. Hematuria
    c. Pain
    d. Fever
4. What diagnostic method is the most effective to detect the kidney cancer?
    a. Laboratory
    b. Ultrasound examination
    c. Palpation
    d. Blood marker

5. What is the hormonal agent used in treatment of the kidney cancer?
   a. Methyltestosterone
   b. Sinestrol
   c. Oksiprogesteron kapronat

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

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THEME 10

PROSTATE CANCER

10.1. EPIDEMIOLOGY

Prostate cancer is the most common malignancy and the second leading cause of cancer death in Western men. It is highly heterogeneous with a disease specific mortality of one in seven. Many men survive decades without treatment, while others succumb quickly despite aggressive management. Among men who require systemic treatment, response rates to therapies are also highly variable-most notably some patients respond to androgen deprivation therapy for decades while a minority do not respond at all. Currently, the combination of clinical stage (tumor size on palpation), serum level of the prostate specific antigen (PSA) , and histological grade (reported as Gleason score) is used to guide treatment decisions. Although useful for some clinical decisions, the modest predictive value of these parameters results both in overtreatment of many man and ineffective treatment for others. To achieve a "personalized medicine" approach to prostate cancer, it is important to define the repertoire of molecular lesions in prostate cancer, to identify the effect of these lesions on disease aggressiveness, and to identify therapies that have specific effectiveness against individual molecular lesions. Precedent for the ultimate success of this approach comes from other malignancies, such as the target specific kinase inhibitors erlotinib and PF-02341066 in lung cancers harboring epidermal growth factor receptor (EGFR) mutations and ML4-ALK fusions, respectively, the anti-HER2 antibody trastuzumab in breast cancers harboring HER2 amplification, and the kinase inhibitor PLX4032 in melanomas harboring BRAF mutations.

In prostate cancer, recent work is beginning to define disease subtypes driven by different oncogenic genetic lesions . Ongoing research is expected to result in a more personalized treatment approach in prostate cancer, including who to screen, who to treat, and what form of treatment to use.

10.2. HISTOPATHOLOGY

Normal prostatic epithelium contains a heterogeneous group of cells representing several distinct levels of differentiation. Epithelial layers are more readily observed in organs such as the skin or colon but are nevertheless present in the normal prostate as well. Secretory luminal cells are well-differentiated epithelial cells that produce PSA and are positive for androgen receptors (ARs). The secretory cells are derived from basal cells through an intermediate proliferating group of cells that are variable in AR and PSA expression. More mature cells in the intermediate pool are positive for AR and PSA, whereas less mature cells in this pool are not. The PSA-producing secretory luminal cells are terminally differentiated and incapable of proliferation (Wang, Hayward t al. 2001; Signoretti and Loda 2006). Rare neuroendocrine cells are also present in normal prostatic epithelium.

More than 95% of malignancies in the prostate are adenocarcinomas that arise in acinar and proximal ductal epithelium. Most tumors arise in the peripheral zone of the prostate but transitional zone tumors are well described.

Other tumors developing in the prostate include intralobular acinar carcinomas, ductal carcinomas, small cell or scirrhous pattern tumors, a rare clear cell variant resembling renal cell carcinomas, and mucinous carcinoma. Small cell tumors of the prostate have neuroendocrine features and are composed of small, round, undifferentiated cells.4 Ductal and small cell tumors are prone to early metastases. Urothelial and rectal cancers may invade the prostate and are occasionally diagnosed during a prostate biopsy as a consequence of DRE abnormalities and/or elevations in PSA. The typical adenocarcinoma of the prostate can be distinguished from other neoplasms using PSA immunohistochemistry. Neuroendocrine differentiation can be assessed by markers such as neuron-specific enolase, synaptophysin, and chromogranin A.

Prostate biopsy specimens occasionally contain proliferative foci of small atypical acini that display some features, but not all, diagnostic of adenocarcinoma, referred to as atypical small acinar proliferation (ASAP).

Prostate cancer has been identified in specimens from subsequent biopsies in up to 60% of cases of ASAP, indicating that this finding is a significant predictor of cancer on subsequent prostate biopsy. Identification of ASAP warrants repeat biopsy for concurrent or subsequent invasive carcinoma. Prostate biopsy specimens may also demonstrate intraductal proliferation, termed prostatic intraepithelial neoplasia (PIN). PIN is defined by the presence of cytologically atypical epithelial cells within architecturally benign-appearing acini and is subdivided into low and high grades? An atrophic but highly proliferative condition associated with chronic inflammation, proliferative inflammatory atrophy (PIA), may in fact be the first histologic step in the carcinogenic process. The epithelial cells in PIA appear to be cycling rapidly based on increased expression of Ki-67 and decreased expression of p27/kipl. Morphologic transitions have been identified between PIA and high-grade PIN in a substantial number of cases, suggesting a causal link between these two entities . Weak expression of PSA and AR, high levels of selected cytokeratins (KS/18), and lack of p63 identify the epithelial cells in PIA as intermediate between the basal and secretory cell phenotype.

Prostatic adenocarcinomas are often multifocal and heterogeneous, a factor that complicates both prognostication and attempts to develop focal therapy. Studies of step-sectioned radical prostatectomy (RP) specimens indicate that most can cers contain multiple grades arranged i n heterogeneous and unpredictable interrelationships. Patients not only have multifocal tumors but also an average of 2.7 different grades of cancer in each specimen; only 10% of index cancers in RP specimens are composed of a single histologic grade. Thus, any diagnostic method short of whole-gland sampling is inevitably subject to sampling error. This is a maj or issue for surveillance protocols. Careful genetic studies indicate that multifocality is typically a function of separately arising tumors rather than intraprostatic tumor spread.

Adenocarcinomas typically stain negative for basal cell markers such as basal-specific cytokeratins and p63, and positive for a-methylacyl-coenzyme A racemase, which is up-regulated in adenocarcinoma cells.

10.3. GLEASON SCORE

The contributions of Gleason are unquestioned with regard to prognosis. Microscopic evaluation of prostate tissue and careful histologic grading, via Gleason scoring or one of several similar alternatives, is one of the most important factors in understanding clinically relevant outcomes in this heterogeneous disease. Every method of risk stratification for patients with localized prostate cancer mcorporates histologic grading (Gleason score or proxy) as one of the most Important variables in determining prognosis. Molecular determmants of Gleason are an area of active study.

Gleason grading evaluates the architectural details of individual cancer glands under low-to-medium magnification. Five distinct patterns of growth from well to poorly differentiated were described in the original Gleason grading scale. Pattern 1 tumors are the most differentiated, with discrete glandular formation, whereas pattern 5 lesions are the most undifferentiated, with loss of the glandular architecture. The final Gleason score is the sum of the grades of the most common and second most common growth patterns; the Gleason score can range from 2 (1+1) to 10 (5+5).

The prognostic importance o f Gleason's scoring system has been difficult to improve on; however, some data suggest that the overall prognosis is driven preferentially by the high-grade components of the tumor. Two notable variations of the original Gleason score have consequently evolved. First, for those cancers that have minor but significant high-grade components, a tertiary Gleason score can be reported (i.e., 3+4=7 with tertiary 5) and this carries significant prognostic mformation.

Second, some investigators have advocated that the percentage of Gleason grade 4/5 cancer be reported as the percentage of high grade is not clearly descnbed by conventional Gleason sums. This is clearly of importance patients with a Gleason score of 7. It is established that Gleason 3 + 4 = 7 tumors vary from Gleason 4 + 3 = 7 cancers with respect to outcomes after various treatments. The full Gleason spectrum is rarely used today. Low-grade tumors (Gleason score of 5 or less) are rarely reported in contemporary series. Re-reading of older prostate cancer specimens in a controlled fashion suggests that contemporary pathologic readings are upgraded relative to those in the past, 17 with Gleason 3 + 3 = 6 bemg the predommant cancer detected in most recent series.

10.4. CLINICAL FEATURES

The need to pursue a prostate cancer diagnosis is most often based on an abnormal screening test, either an abnormal DRE or more commonly an abnormal PSA level.

Any palpable abnormality should be pursued, but only 25% to 50% of men with an abnormal DRE prove to have prostate cancer. Similarly, a normal DRE does not exclude the presence of cancer.

Symptoms from prostate are rarely present at the time of diagnosis. Local symptoms from prostate cancer usually do not manifest until invasion of the periprostatic tissue has occurred, at which point curative therapy is usually not possible. Therefore, the opportunity to cure prostate cancer depends on detection prior to onset of symptoms. The most common symptom of prostatic disease in men older than 50 years is bladder outlet obstruction, including hesitancy, nocturia, incomplete emptying, and a diminished urinary stream. Their occurrence, although more commonly related to BPH, should prompt a careful DRE and PSA determination. Today, men rarely present with symptoms of metastatic disease such as bone pain, anemia, or pancytopenia from bone marrow replacement, involvement, or disseminated intravascular coagulation.

The diagnosis is established by a TRUS-guided transrectal needle biopsy. TRUS is most useful to target sites for needle biopsy in the prostate and to determine prostate volume. TRUS is not used for routine screening for prostate cancer, but in a man undergoing an evaluation of an elevated PSA and/or an abnormal DRE, TRUS findings can help direct where biopsies are taken. Cancers are typically hypoechoic relative to the normal peripheral zone, although there is no pathognomonic imaging finding that predicts cancer with certainty. The needle biopsy procedure is performed transrectally with an 1 8 -gauge needle mounted on a spring-loaded gun directed by ultrasound. Any palpable abnormality on DRE should be targeted for biopsy using finger guidance. In addition, abnormal areas visible on TRUS should be sampled, along with a total of at least ten systematic biopsies of the prostate taken from the left and right apex, middle, and base of the peripheral zone. Each core should be identified separately as to location and orientation so that the pathologist can report the extent and grade of cancer in each core and the presence of any perineural invasion or extraprostatic extension.

10.5. DIAGNOSTICS
Clinical Stage and DRE
The DRE is critical to establishing the clinical stage of the cancer. An assessment of the location, size, and extent of the primary cancer provides prognostic information and is essential for treatment planning. Although not uniformly accurate, DRE provides some evidence of the cancer's size and pathologic stage and correlates to some degree with prognosis.

The overwhelming maj ority of men diagnosed with prostate cancer today do not present with metastases that can be detected by imaging studies.

Patients with clinically localized cancer (T1-T2) have a low probability of metastases detectable by current diagnostic tests, such as bone scan, computed tomography (CT), or magnetic resonance imaging (MRI), unless the serum PSA level and/or the biopsy Gleason sum are high. Consequently, most patients diagnosed with a clinically localized prostate cancer need no further studies to rule out metastases. Patients with very aggressive tumors (PSA >20 ng/mL and biopsy Gleason score > 7), advanced local lesions (T3-4), or symptoms suggestive of metastatic disease should have imaging studies, including a bone scan.

Transrectal Ultrasound

Ultrasound is the standard imaging tool used by urologists to initially assess the prostate and assist in the guidance of needles for directed tissue biopsies to establish a diagnosis. The sensitivity of TRUS-guided biopsies is reported to be 70% to 80%. Cancers appear hypoechoic on TRUS compared with the normal-appearing peripheral zones of the prostate. In addition to its function to establish tissue diagnosis, TRUS is also useful in assessing the volume of the prostate and calculating the PSA density. The latter is calculated by dividing the PSA value in nanograms per milliliter by the volume in cubic centimeters obtained on TRUS . Limitations of this imaging modality include the difficulty characterizing the integrity of prostatic capsule and visualizing early extraprostatic extension (EPE) or seminal vesicle involvement. Color duplex and power Doppler have been used to further improve the specificity of TRUS by enhancing regions within the prostate with associated hypervascularity that often corresponds to tumor activity.

Computerized Tomography

Computerized tomography (CT) scans of the pelvis are commonly used by many practitioners in the workup of prostate cancer, but they possess limited capabilities in the detection of intraprostatic disease and quantification of EPE and seminal vesicle involvement (SVI). CT scans are more helpful to detect lymph node metastases within the pelvis, yet there has been a wide range of reported sensitivities and specificities for nodal detection with CT scanning.

Magnetic Resonance Imaging

With current magnet strengths of 1.5 Tesla, the endorectal coil together with a pelvic array coil provides the most optimal imaging to appreciate the prostate anatomy. On T1 -weighted images the prostate is homogenous in intensity and tumors are difficult to appreciate. On T2-weighted images prostate tumors have decreased signal intensity relative to the higher signal intensity characteristic of the normal-appearing peripheral zone.

There are varying opinions as to the value of magnetic resonance imaging (MRI) in routine staging and imaging of the prostate, and broad variations in the specificity and sensitivity for the detection for EPE and SVI have been reported.

In general, MRI permits better visualization of the prostatic capsule to assess for evidence of EPE or SVI, taking advantage of transverse, sagittal, and coronal images for providing greater anatomic detail.

Magnetic resonance spectroscopy uses in vivo proton spectroscopy of the prostate to detect the relative concentrations of choline, creatine, and citrate within defined regions of the prostate. Normal prostate tissue displays citrate while prostate cancer, because of greater cell membrane degradation, contains higher levels of choline and lesser concentrations of citrate. The greater choline-to-citrate ratios observed in tumors have been shown to correlate as well with a higher likelihood of the presence of high-grade cancer.

The addition of spectroscopy to MRI appears to improve the ability to localize disease more precisely and reduces the degree of interobserver variability, but this form of imaging has yet to become the standard of care. Diffusion-weighted imaging is a promising functioning imaging modality that takes advantage of the known variability of random movements of water molecules observed between normal tissues and tumors. The rate of diffusion of water molecules is more restricted within tumors than in normal tissues and allows for an important metric known as the apparent diffusion coefficient. In one study comparing MRI with combined MRI and diffusion-weighted MRI, the sensitivity and specificity were 86% and 84%, respectively.

Dynamic contrast-enhancement MRI may provide further diagnostic information regarding presence of disease, as various quantitative parameters can be derived from contrast-time curves that have been shown by some to correlate with presence of cancerous tissue. In one study, the combination of T2-weighted imaging in conj unction with dynamic contrastenhancement MRI finding had sensitivity and specificity rates of 77% and 91% for detecting tumor foci that measured 0.2 cm^3, but these values improved to 90% and 88%, respectively, when detecting tumors greater than 0.5 cm^3.

Bone Scan

Radionuclide bone scan is the standard imaging study to assess for the presence of osseous metastases. Because of the low yield in low-risk patients (baseline PSA levels <10 ng/mL), bone scan is unnecessary and not recommended. It has been noted that for patients with PSA levels of less than 10, the incidence of a positive bone scan is less than 1%, while for patients with PSA levels between 10 and 50 and greater than 50 ng/mL, the incidence of positive bone scans is 10% and 50%, respectively. Bone scanning is frequently used to assess the response of hormonal therapy and chemotherapy for those with metastatic disease.

ProstaScint Scanning

Radioimmunoconj ugates using monoclonal antibodies are currently undergoing intense investigation for imaging tumor in both soft tissue and bone.

The commercially available ProstaScint scan is used most frequently in patients with rising PSA levels after primary therapy to help determine whether relapse is local or systemic. Although ProstaScint is helpful in some cases, nonspecific localization to the gastrointestinal (GI) tract may be interpreted incorrectly as metastatic disease. In addition, the interpretation of the scan is subject to interobserver variability, and the results.

Positron Emission Tomography

Fluorine 1 8 fluorodeoxyglucose has been the most commonly used radioisotope for imaging of prostate cancer. In most studies to date, the sensitivity for prostate imaging in patients with localized disease has been poor. Positron-emitting tomography-CT imaging has significantly improved the ability to discern intraprostatic disease and lymph node metastases. Newer tracers including carbon 11 methionine, C11 acetate, and C11 choline may be more valuable for imaging and will require prospective clinical evaluation.

10.6. TNM-CLASSIFICATION

T – Primary Tumour

TX   Primary tumour cannot be assessed
T0   No evidence of primary tumour
T1   Clinically inapparent tumour, neither palpable nor visible by imaging
T1a   Tumour incidental histological finding in 5% or less of tissue resected
T1b   Tumour incidental histological finding in more than 5% of tissue resected
T1c   Tumour identified by needle biopsy, e.g., because of elevated prostate-specific antigen (PSA)
T2   Tumour confined within prostate[1]
T2a   Tumour involves one-half of one lobe or less
T2b   Tumour involves more than one-half of one lobe, but not both lobes
T2c   Tumour involves both lobes
T3   Tumour extends through the prostatic capsule[2]
T3a   Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b   Tumour invades seminal vesicle(s)
T4   Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall

Notes: 1. Tumour found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.
2. Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

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
M1a   Non-regional lymph node(s)
M1b   Bone(s)
M1c   Other site(s)
*Note: *When more than one site of metastasis is present, the most advanced category is used. pM1c is the most advanced category.*

G Histopathological Grading
GX   Grade cannot be assessed
G1   Well differentiated (slight anaplasia) (Gleason 2–4)
G2   Moderately differentiated (moderate anaplasia) (Gleason 5–6)
G3-4 Poorly differentiated/undifferentiated (marked anaplasia) (Gleason 7–10)

Group staging

Stage	T	N	M
I	T1	N0	M0
I	T2a	N0	M0
II	T2b	N0	M0
II	T2c	N0	M0
III	T3	N0	M0
IV	T4	N0	M0
IV	Any T	N1	M0
IV	Any T	Any N	M1

10.7. TREATMENT

TREATING CLINICALLY LOCALIZED PROSTATE CANCER
        The clinical course of newly diagnosed prostate cancer is difficult to predict. Men with similar clinical stage, serum PSA levels, and biopsy features can have markedly different outcomes. Although prostate cancer is unequivocally lethal in some patients, most men do indeed die with, rather than of, their cancer. The challenge to physicians today is to identify the minority of men with aggressive, localized prostate cancer with a natural history that can be altered by definitive local therapy, while sparing the remainder the morbidity of unnecessary treatment.

Identifying Low-Risk Prostate Cancer

Many physicians and patients consider AS for selected lowrisk prostate cancers; the difficulty is defining "low risk." Initial clinical staging (DRE), PSA, and diagnostic biopsy results have limited potential for accurately characterizing localized prostate cancers, although systematic needle biopsies serial PSA determinations, and modern imaging are promising tools for more accurately assessing the size, grade, and extent of the cancer.

In an attempt to identify patients with low-risk cancers, Epstein et al. examined preoperative clinical and biopsy features in 157 men with clinical stage T1c prostate cancer who underwent RP to find features that could predict insignificant tumors-defined as organ-confined cancers with a total tumor volume less than 0.2 cm^3 and a pathologic Gleason sum 6 or less in the RP specimen. Their model for predicting an insignificant cancer included no Gleason grade of 4 or 5 in the biopsy specimen and either:

- PSA density of 0 . 1 ng/mL per gram or less, fewer than three biopsy cores involved with cancer (minimum of six cores obtained), and no core with more then 5 0 % involvement, or
- PSA density of 0 . 1 5 ng/mL per gram or less and on only one (of six or more) biopsy core with cancer smaller than 3 mm.

As a test for insignificant disease, this model had a negative predictive value of 95% and a positive predictive value of 66% in their own data set. Most physicians use some modification of the previously mentioned "Epstein criteria" to identify potential candidates for AS. Since this initial report, a number of investigators have developed algorithms for predicting low-risk prostate cancer.

Because patient selection for AS is critically dependent on the results of the prostate biopsy (Gleason grade and amount of cancer) , some investigators have suggested more extensive biopsy strategies to better assess the true extent of cancer within the prostate. TRUS-guided prostate biopsy has been shown to poorly reflect the grade and extent of a patient's cancer when compared with the RP specimens. Crawford et al., using computer simulations on autopsy and RP specimens, suggested that transperineal prostate biopsies using a brachytherapy template, spaced at 5-mm intervals throughout the volume of the prostate, could determine grade and detect significant cancers with greater sensitivity. Onik and Barzell used a transperineal three-dimensional (3D) mapping method to restage 110 patients, all of whom had had unilateral prostate cancer diagnosed by TRUS biopsies. The median number of cores taken was 46 (SD±19). Bilateral cancer was found in 60 patients (55%) and the Gleason score was increased in 25 (23%). Complications were self-limited and included nine patients (8%) who required short-term catheterization and two (2%) with hematuria. Although this study was primarily designed to assess the role of transperineal biopsy in selecting men for focal therapy, the investigators hypothesized that 75% of patients thought to have low-risk cancers eligible for AS were found to have larger, higher-grade tumors better treated with definitive therapy.

Although extensive biopsy strategies provide more information than a standard TRUS-guided biopsy does, their role in routinely evaluating a patient for AS is unclear.

None of the commonly used guidelines for identifying candidates for AS have relied on extended prostate biopsy. Further information is needed before a routine recommendation for this procedure is embraced.

Radical Prostatectomy

RP is recommended only for patients with clinically localized prostate cancer (cT1-T3a, N0 or Nx, M0 or Mx) and a life expectancy of 10 or more years. Because of the risk inherent in major surgery, it should be reserved for patients with little or no systemic comorbidity. Although the risk of recurrence after RP rises with higher clinical stage, Gleason grade, and serum PSA level, no absolute cutoff values exclude a patient as a candidate. Perhaps the most compelling evidence that selected patients with prostate cancer benefit from active treatment compared to watchful waiting comes from a Scandinavian trial that randomized 695 men with clinically localized prostate cancer to either RP or watchful waiting with systemic treatment deferred until the development of symptomatic progression.

The primary end point of this study was death from prostate cancer. During a median follow-up of 8.2 years, 50 of the 348 men assigned to watchful waiting died from prostate cancer, compared with 30 of the 347 men assigned to RP (relative hazard, 0.56; 95% confidence interval [CI]: 0.36-0.88; P=.01). The men assigned to surgery had a lower relative risk of distant metastases than the men assigned to watchful waiting (relative hazard, 0.60; 95% CI: 0.42-0.86). For men who were managed conservatively, the cumulative probability of developing metastatic disease 10 years after diagnosis was 25% and the cancer-specific mortality rate was 15%. Most importantly, there was an absolute and statistically significant increase in overall survival at 10 years for patients in the surgery arm.

This elegant study firmly documents the overall benefit of RP in patients with clinically localized prostate cancer diagnosed in the absence of systematic screening. The relevance of this study to cancers detected by screening, which may be much earlier in their natural history, is uncertain.

Surgical Technique. The goals of modern RP are to remove the entire cancer with negative surgical margins, minimal blood loss, no serious perioperative complications, and complete recovery of continence and potency. Achieving these goals requires careful surgical planning. As no single test provides a reliable estimate of the size, location, and extent of the cancer, we rely on the results of DRE, serum PSA levels, and a detailed analysis of the amount and grade of cancer in each individually labeled biopsy core, along with the results of the TRUS or the endorectal coil MRI.

The results are used to plan the steps necessary to remove the cancer completely and to assess the likelihood that one or both of the neurovascular bundles will have to be resected partially or fully to minimize the risk of a positive surgical margin. The retropubic procedure is performed through either a suprapubic incision (open RP) or using a minimally invasive (laparoscopic or robot-assisted laparoscopic) approach.

<u>Selecting Patients for Pelvic Lymph Node Dissection</u>

Without exception, men whose cancer has spread to the pelvic nodes have a significantly worse prognosis than men with negative pelvic lymph nodes. Even so, controversy persists concerning the role of pelvic lymph node dissection (PLND) in treating patients with locally advanced disease. A number of investigations have found the incidence of lymph node metastasis in patients considered to have low-risk prostate cancer (clinical stage T1c, preoperative PSA values <10 ng/mL, and a prostate biopsy Gleason score 6) to be as low as less than 5%. Thus, some surgeons consider PLND unnecessary in these low-risk patients.

However, these reports may underestimate the true likelihood of lymph node metastases because they generally are based on a limited lymph node dissection (external iliac nodes only). In men undergoing RP with full extended PLND who have a PSA less than 10 ng/mL, the rate of nodal involvement ranges from 11% to 17%. This incidence increases with increasing Gleason score. Schumacher et al. reported that patients with Gleason score of 7 or more on surgical pathology had a 25% chance of positive nodes, whereas only 3% with a Gleason score of 6 or less were nodepositive.

These relatively high rates of lymph node metastasis stand in contrast to other published series, probably because of the extent of PLND performed, the diligence of the pathologist in reviewing the surgical specimen, and more advanced stage of cancers in the European series where screening was less intense than in the United States. Surgical studies have confirmed that nodal metastases in 15% to 30% of patients may be detected exclusively in areas outside the boundaries of a limited dissection. Our current practice is to restrict PLND at the time of RP to men with a 2% or more risk of positive nodes according to a contemporary nomogram.

<u>Radical Prostatectomy</u>

RP is one of the most complex operations performed by urologists. It challenges surgeons to obtain results that are exquisitely sensitive to fine details in surgical technique. The elusive goals of RP are to remove the cancer completely with negative surgical margins, minimal blood loss, no serious perioperative complications, and complete recovery of continence and potency. No surgeon achieves such results uniformly.

Technical refinements have resulted in lower rates of urinary incontinence and higher rates of recovery of erectile function, less blood loss and fewer transfusions, shorter hospital stays, and lower rates of positive surgical margins. A thorough understanding of periprostatic anatomy and vascular control by contemporary surgeons further increases the probability of a successful RP with reduced morbidity.

<u>Open Radical Prostatectomy</u>
<u>Acute Postoperative Complications.</u>

With refinements in anesthesia, perioperative care and surgical technique, blood loss, length of hospital stay, complications, and mortality after open surgery have decreased over time. The mortality rate ranges from 0.16% to 0.66% in modern series, rising with increasing age and comorbidity. Deep venous thrombosis and pulmonary embolism occur in approximately 2% of cases, with little evidence that anticoagulants or sequential pneumatic compression are preventive. Early ambulation, a short hospital stay, and use of epidural anesthesia are probably responsible for the lower rate of thromboembolic events. Rectal injuries are uncommon. Standardized treatment pathways have been shown to decrease the cost of radical retropubic prostatectomy without compromising quality of care. Hospital stays now average less than 3 days for open RP and 1 to 2 days for laparoscopic RP (LRP), with or without robotic assistance.

EXTERNAL-BEAM RADIOTHERAPY
<u>Conformal and Intensity-Modulated Radiation Therapy and ImageGuided Techniques</u>

With the advent of 3D conformal radiotherapy (3D-CRT) in the late 1980s, the precision of radiotherapy significantly improved compared with standard conventional techniques. With 3D-CRT, CT-based images referenced to a patient immobilized in the treatment position are used to localize the prostate and surrounding normal tissue structures to generate high-resolution 3 D reconstructions of the anatomy. These approaches facilitated the ability to deliver safely higher radiation doses to the prostate, paving the way for critical dose-escalation studies.

Intensity-modulated radiotherapy (IMRT) can be considered as second-generation 3D-CRT, which takes advantage of sophisticated computeraided optimization algorithms to produce dose distributions that conform even more precisely to the tumor target.

Although 3D-CRT relies on trial-and-error forward-planning techniques to create a treatment plan, IMRT takes advantage of inverse-planning methods used for optimization of the dose distribution. Inverse planning is part of a mathematical optimization algorithm that creates a treatment plan based on predefined desired dose-distribution parameters for the target and dose constraints imposed on the normal tissues.

The highly conformal radiation beam is produced with the ability of IMRT to vary the intensities of the x-rays from each treatment field over the entire crosssection of the beam. Tomotherapy is another approach used to achieve varying intensity beam profiles using x-rays directed over a full 360-degree range, modulated by a slit, bimodal multileaf collimation.

<div align="center">Trus-Guided Prostate Brachytherapy</div>

Excellent long-term tumor control can be achieved with brachytherapy, and this approach is considered a standard treatment intervention associated with comparable outcomes to prostatectomy and EBRT for patients with clinically localized disease. In general, for patients with low-risk disease, seed implantation alone achieves high rates of biochemical tumor control and cause-specific survival outcomes. For those with intermediate risk and selected high-risk disease, a combination of brachytherapy (low-dose-rate permanent interstitial implantation, or highdose-rate brachytherapy via after-loading catheters) with EBRT is commonly used. Whether the addition of EBRT is necessary in all patients with intermediate-risk prostate cancer is currently being studied in a phase 3 randomized trial (RTOG-0232).

10.8. QUESTIONS FOF SELF-CONTROL
1. What causes prostate cancer?
2. How common is prostate cancer?
3. Can prostate cancer be prevented?
4. What are the risk factors for prostate cancer and who is at risk?
5. How is prostate cancer treated?

10.9. TESTS FOR SELF-CONTROL

1. The risk factors of prostate cancer include…
   a. Being of African descent
   b. Being under 50 years of age
   c. Having a first-degree relative who has been diagnosed with prostate cancer
   d. 1&3
2. Common prostate cancer symptoms include:
   a. Slow urinary stream
   b. Frequent urination
   c. Problems during sexual intercourse
   d. All of the above
3. Which of following tests confirm cancer of the prostate:
   a. PSA test
   b. DRE Screening

      c. Biopsy of the prostate gland
      d. Gleason scores
4. What is a red-alert reading on PSA test?
      a. 2-4 ng/mL
      b. 4-6 ng/mL
      c. 7-9 ng/mL
      d. over 10 ng/mL
5. Non-cancerous Enlargement of the prostate is termed:
      a. Prostatitis
      b. Benign Prostatic Hyperplasia
      c. Prostate cancer
      d. None of the above

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

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