

Ministry of Public Health of Ukraine
Kharkov National Medical University

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Textbook

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Clinical oncology: Textbook – Kharkov, 2013. – 206p.

This textbook contains 16 units on common cancer localizations. Each unit describes incidence, risk factors, epidemiology, histology, clinical presentation, clinical classification, diagnosis, treatment, disease prognosis. Questions for self control and tests are given at the end of each unit.

This textbook is intended for the 5th – 6th year English medium students of medical universities. This was compiled with ECTSsystem.

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Клінічна онкологія: Підручник – Харків, 2013. – 206с.

Цей підручник має 16 тем. У підручнику викладено загальні принципи діагностики та лікування злоякісних пухлин, зокрема раку легені, стравоходу, шлунка, підшлункової залози, кішківника, жіночих статевих органів, сечової системи, кісток, м'яких тканин тощо. Кожна тема описує епідеміологію, гістологію, клінічну картину, клінічну класифікацію, діагноз, лікування, прогноз хвороби і випробування.

Цей підручник призначається для англomовних студентів 5 та 6 курсів. Навчальний посібник відповідає вимогам Болонської системи навчання з онкології і розрахований на студентів медичних вузів III – IV рівнів акредитації.

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Approved by the Academic Council of Kharkov National Medical University and is recommended for the 5th and 6th year students of medical faculty.

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CONTENTS

| | |
|--|-----|
| Introduction..... | 4 |
| 1. Lip and oral cavity cancer..... | 5 |
| 2. Laryngeal cancer..... | 14 |
| 3. Esophageal cancer..... | 22 |
| 4. Gastric cancer..... | 29 |
| 5. Liver cancer..... | 37 |
| 6. Pancreatic cancer..... | 46 |
| 7. Colorectal cancer..... | 56 |
| 8. Lung cancer..... | 66 |
| 9. Breast cancer..... | 81 |
| 10. Thyroid cancer..... | 98 |
| 11. Skin tumors (Skin cancers (BCC, SCC))..... | 110 |
| 12. Malignant lymphomas | 130 |
| 13. Soft tissue and bone tumors..... | 142 |
| 14. Cancer of kidney, ureter, urinary bladder..... | 163 |
| 15. Gynecologic tumors (uterine cancer, cervical cancer, ovarian cancer)..... | 178 |
| 16. Prostate cancer..... | 196 |

INTRODUCTION

Oncology is the science that deals with tumors, the causes and conditions of their etiology and the mechanism of their onset, preventive measures, diagnosis, and treatment. The problem of malignant neoplasms is the central one. The scientists from different countries of the world try to work out a scientifically based strategy of fight against cancer.

Progress in fundamental, experimental and clinical researches has given the growth in knowledge and possibility to improve the diagnosis and thus the results of cancer patients treatment.

Only comprehension of tumor biology and possession of information about recent achievements in the field of oncology underlie understanding multistage carcinogenesis and provide further support for new research strategies to prevent and treat cancer.

This knowledge helps clinicians in their daily task in treating patients.

The causes of malignant tumors development are of great interest and their prevention depends on the patient himself.

There is strong possibility that preventive approaches may greatly impact cancer incidence.

Primary cancer prevention, early diagnosis and improvement in cancer patients treatment results in mortality decrease. This book presents up - to - date information concerning diagnosis, classification, cancer patients treatment, and perspective directions of development in this field of medicine.

Each unit of this book is concluded by questions for self control and tests.

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LIP AND ORAL CAVITY CANCER

The most common sites of oral cancer are lower lip, lateral marginal of the tongue and floor of the mouth.

I. Lower lip cancer.

Carcinoma of the lip is second only to skin cancer as a site of neoplasia within the head and neck region. Lower lip cancer concerns to number common cancer diseases, and top lip cancer is extremely rare.

In Ukraine the incidence was 2.1 persons per 100.000 population in 2012 year (in men 3.3, in women 1.1 cases).

Risk factors

- Smoking – 90%. Use of tobacco, pipes and cigars.
- High insolation (peasants).
- Wind exposure.
- Xeroderma pigmentosum.
- White spot (leukoplakia).
- Papilloma.
- Chronic splits.
- Skin horn.
- Keratoacantoma.
- Erythroplakia.

Histological classification

- Squamous cell carcinoma is the principal cancer involving the lip.
- Basal cell carcinoma is the other lip lesion.
- Minor salivary gland cancer occurs rarely.

Clinical presentation (Fig. 1,2)

95% of lip cancer occur on the lower lip. The symptoms usually are:

- Sore.
- Scab.
- Ulcer.
- Bleeding or pain.

- Numbness of the skin of the chin is the result of mental nerve involvement.



Fig. 1. Low lip tumor clinical presentation



Fig. 2. Low lip tumor clinical presentation

Classification of lower lip cancer by TNM system

T - Primary tumor

- TX: Primary tumor cannot be assessed.
- T0: No evidence of primary tumor.
- Tis: Carcinoma in situ.
- T1: Tumor ≤ 2 cm in the greatest dimension.
- T2: Tumor > 2 cm but ≤ 4 cm in the greatest dimension.
- T3: Tumor > 4 cm in the greatest dimension.
- T4: (lip)Tumor.

- T4a
- T4b

N - Regional lymph node involvement

- NX: Regional lymph nodes cannot be assessed.
- N0: No regional lymph node metastases.
- N1: Metastasis in a single ipsilateral lymph node, ≤ 3 cm in the greatest dimension.
- N2: Metastasis in a single ipsilateral lymph node, > 3 cm but ≤ 6 cm in the greatest dimension.
- N2a: Metastasis in a single ipsilateral lymph node, > 3 cm but ≤ 6 cm in the greatest dimension.
- N2d: Metastasis in multiple ipsilateral lymph nodes ≤ 6 cm in the greatest dimension.
- N2c: Metastasis in bilateral or contralateral lymph nodes ≤ 6 cm in the greatest dimension.
- N3: Metastasis in a lymph node > 6 cm in the greatest dimension. Most masses > 3 cm in diameter are not single nodes but confluent nodes or tumors in soft tissues of neck. Midline nodes are considered homolateral nodes.

M - Metastatic involvement

- MX: Distant metastasis cannot be assessed.
- M0: No distant metastasis.
- M1: Distant metastasis.

Grouping of lower lip cancer in stages

- **Stage 0** Tis, N0, M0
- **Stage I** T1, N0, M0
- **Stage II** T2, N0, M0
- **Stage III** T3, N0, M0
 T1, N1, M0
 T2, N1, M0
 T3, N1, M0
- **Stage IVA** T4a, N0, M0
 T4a, N1, M0
 T1, N2, M0
 T2, N2, M0
 T3, N2, M0

T4a, N2, M0
Stage IVB any T, N3, M0
T4b, any N, M0
Stage IVC any T, any N, M1

Diagnosis

- Inspection.
- Palpation.
- Direct endoscopy when necessary.
- Biopsy is essential to confirm the diagnosis.
- MRI (Magnetic Resonance Imaging).
- CT scan (Computer Tomography).
- Morphological verification.

Treatment:

Treatment choice depends on the stage of disease.

- Stage T1 to T3 squamous cell lip carcinomas are managed by radiation therapy or surgery.
- It depends on the size and location of disease.
- If the lesion is small, surgery is chosen.
- Brachytherapy is used in patients with early T1 and small T2 lesions.
- Stage III and IV lip cancers are managed with combined surgery and postoperative radiation therapy.
- Radiation therapy alone:
 - external-beam radiation therapy;
 - interstitial implantation;
 - combination of these therapies.

Prognosis

Prognosis from lip cancer depends on the size of the primary tumor.

A 5 year survival:

T1 lip cancer - 90%,

T2 lip cancer - 84%.

In patients with lymph node metastases survival is 50%. Prognosis is worse in younger adults.

II. Oral cavity cancer (OCC). The frequency of this pathology made 5.7 persons per 100 000 population in 2011 year, (in men – 9.8, in woman 2.1); in 2012 year it was 5.5 persons per 100.000 population, (in men 9.4, in women 2.1). The ratio of men to women is approximately 5:1 and basically in patients of 60 -70 years.

Oral cavity cancer sites are:

- Tongue (lateral part) - 70%. (Excluding the lip, the tongue exceeds all other sites in the oral cavity).
- Floor of the mouth – 10%.
- Gingival – 5%.
- Hard and soft palate – 7%.
- Buccal mucosa – 5%.

Risk factors :

- Xeroderma pigmentosum.
- Franconia anemia.
- Tobacco smoking – 90%.
- Tobacco chewing (marijuana smoking).
- Conception of alcohol.
- Poor dental hygiene.
- Tongue injury (biting of the tongue with false tooth) – lateral surface.
- Papillomas.
- Chronic wounds.
- Leukoplakia.
- Syphilis.
- Diet (vitamin A deficiency)
- Chronic irritants (mouthwash).
- Human Papilloma Virus (HPV)

Clinical presentation

- Scab covered ulcer.
- Local pain.

- Stinking smell from the mouth.
- Slurring of speech.

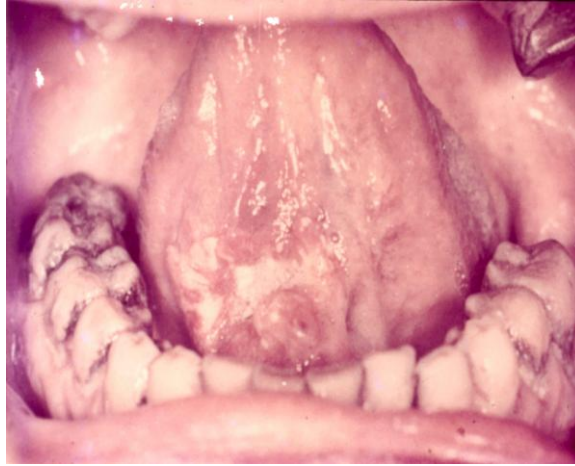


Fig. 3. Tongue tumor clinical presentation



Fig. 4. Tongue tumor clinical presentation

Classification of oral cavity cancer by TNM system

T – primary tumour

T0 – no primary tumor;

Tis – carcinoma in situ;

T1 – tumor up to 2cm or smaller;

T2 – tumor 4 cm or smaller;

T3 – tumor larger than 4 cm;

T4 – tumor larger than 4 cm and deep invasion to muscle, bone, or deep structures, e.g. antrum;

N - regional lymphatic nodes

N0 – no nodes;

N1 – single homolateral node smaller than 3cm;

N2 – nodes homolateral smaller than 6cm;

N3 – nodes larger than 6cm and/or bilateral;

M – distant metastases

M0 – no metastasis;

M1 – metastasis noted.

Grouping of oral cavity cancer in stages

I Stage T1 N0 M0

II Stage T2 N0 M0

III Stage T3 N0 M0, T1-3 N1 – 2 M0

IV Stage T4 N0 M0; any T N2 or N3 M0; any T any N M1

Diagnosis

- History (anamnesis).
- Palpation.
- Cytomorphologic examination.
- Serologic reactions.
- Microscopic examination (smear, scrape, biopsy).

Treatment

Patients with stage I are managed by combined preoperative radiation therapy and surgery. Patients with stage II and regional lymph nodes involvement are managed as in stage I and surgical excision.

stage III – radiation therapy and surgery.

stage IV – palliative radiation therapy.

- Hemiresection of the tongue.
- Lymphodissection of regional nodes.
- Radiation therapy.
- Chemotherapy (cisplatin, 5 – fluorouracil, methotrexate).

Prognosis

The prognosis of OSCC (Oral Cavity Squamous Cell Carcinoms) is site dependent. For intraoral carcinoma, the 5 – year survival rate may be as low as 30% for posterior lesions presenting late, as they often do. The overall 5 – years survival rate is more than 70%.

Questions for self control

1. What is lower lip cancer?
2. How is lower lip cancer diagnosed?
3. What are the risk factors for lower lip cancer?
4. What are the symptoms of lower lip cancer?
5. Methods of diagnosis verification.
6. What are the risk factors for oral cavity cancer?
7. Methods of diagnosis verification for oral cavity cancer.

Tests (choose the correct option)

- 1. The most common site for oral cancer is:**
 - a) lower lip;
 - b) upper lip;
 - c) floor of the mouth;
 - d) distal margin of the tongue.
- 2. Prognosis is worse in:**
 - a) men;
 - b) women;
 - c) children
 - d) younger adults.
- 3. The principal cancer involving the lip is:**
 - a) adenocarcinoma;
 - b) squamous cell carcinoma;
 - c) basal cell carcinoma;
 - d) mucoepidermoid cancer;
 - e) lip traumatize.

- 4. What is the most common risk factor of oral cavity cancer?**
- a) alcohol abuse;
 - b) human papilloma virus;
 - c) cigarette smoking;
 - d) exposure to ionizing irradiation.
- 5. Oral cavity cancer is histologically confirmed by:**
- a) MRT;
 - b) CT of the head;
 - c) Head X – ray;
 - d) biopsy.

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

LARYNGEAL CANCER

Incidence

Cancer occurs in the larynx 13 times less frequently than in the breast, and 9 times less frequently than in the prostate gland.

The given pathology in Ukraine made 5.2 persons per 100 000 population in 2012 year (in men 10.8, in women 0.4 cases). The highest incidence of laryngeal cancer (LC) is observed in men aged 40 – 60, it makes 80 – 95% of patients.

Laryngeal cancer is diagnosed in the patients with stage III of disease (43.4% of the cases in Ukraine).

Larynx anatomic regions

The larynx consists of three subsites, which are the glottis (paired true vocal cords), the supraglottis, and the subglottis.

- The supraglottis is the portion above the glottis, consisting of the epiglottis, false vocal cords and aryepiglottic folds.
- The glottis consists of mobile true vocal cords and the anterior and posterior commissures.
- The subglottic region begins about 1 cm below the cricoid cartilage or the first tracheal ring.

Risk factors

The disease most commonly affects middle aged or older men who have smoked tobacco and have drunk alcohol. The peak incidence of laryngeal cancer is in the sixth decade. The disease rarely occurs in young people.

The following etiological factors have been implicated in laryngeal cancer: voice abuse and chronic laryngitis, certain dietary factors, chronic gastric reflux, and exposure to wood dust, nitrogen mustard, asbestos, and ionizing radiation; cyst, papilloma, fibroma, pachydermy, leukoplakia.

Clinical presentation

Early stage supraglottic larynx is asymptomatic. Then subtle symptoms occur: pain perceived in the ear (otalgia), a scratchy sensation when swallowing.

Advanced disease symptoms: airway alteration, hoarseness, tendency to aspirate liquids. Cancers of the glottis can be often detected early, because of the fact that even a slight change of the vibratory surface of the vocal cords results in voice change.

Subglottic cancers are uncommon. They are asymptomatic at early stages, but disease is usually advanced at the time of diagnosis.

Prognosis factors

- Sex.
- Age.
- Increasing T stage.
- Increasing N stage.
- Performance status.
- Pathologic features of the tumor (grade and depth of invasion).

Pathology

Histological classification:

- Squamous cell subtypes (a variety of nonsquamous cell laryngeal cancers also occur) – 98%.
- Keratinizing.
- Nonkeratinizing.
- Well – differentiated.
- Poorly differentiated grade.
- Glandular.
- Fibrosarcoma.
- Angiosarcoma.
- Rabdosarcoma.

Patterns of growth:

- Exophytic (papilla).
 - Endophytic (infiltrative).
 - Mixed.
- } have poor prognosis.

Diagnosis

- Anamnesis (history).
- Palpation (crepitation symptom).
- Larynx inspection.
- Laryngoscope (both indirect mirror examination and direct endoscope when necessary).
- Flexible endoscopes.
- Direct endoscope when necessary.
- Biopsy (for histological confirmation).
- Head and neck MRT.
- CT.
- Radionuclide I³² diagnoses.

Detection of metastatic disease:

- Liver function tests.
- Chest X – ray.
- Liver ultrasound scan.
- Brain CT.

Classification of Laryngeal cancer by TNM system

Primary tumor (T)

- TX: Primary tumor cannot be assessed.
- T0: No evidence of primary tumor.
- Tis: Carcinoma in situ.

Supraglottis:

- T1 - Tumor limited to one subsite of supraglottis with normal vocal cord mobility.
- T2 - Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa

of the base of the tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx.

- T3 - Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues.

T4 - Tumor invades through the thyroid cartilage, and/or extends into soft tissues of the neck, thyroid, and/or esophagus.

Subsites include the following:

- ventricular bands (false cords)
- arytenoids
- suprahyoid epiglottis
- infrahyoid epiglottis
- aryepiglottic folds (laryngeal aspect)

Glottis:

- T1 - Tumor limited to vocal cord(s) (may involve anterior or posterior commissure) with normal mobility.
- T1a - Tumor limited to one vocal cord.
- T1b - Tumor involves both vocal cords.
- T2 - Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility.
- T3 - Tumor limited to the larynx with vocal cord fixation
- T4 - Tumor invades through the thyroid cartilage and/or to other tissues beyond the larynx (e.g., trachea, soft tissues of neck, including thyroid, pharynx).

Subglottis:

- T1 - Tumor limited to the subglottis.
- T2 - Tumor extends to vocal cord(s) with normal or impaired mobility.
- T3 - Tumor limited to larynx with vocal cord fixation.
- T4 - Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (e.g., trachea, soft tissues of neck, including thyroid, esophagus).

Regional lymph nodes (N)

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

- N1 - Metastasis in a single ipsilateral lymph node, 3cm or less in the greatest dimension.
- N2 - Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in the greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in the greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in the greatest dimension.
- N2a - Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in the greatest dimension
- N2b - Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in the greatest dimension.
- N2c - Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in the greatest dimension.
- N3 - Metastasis in a lymph node more than 6 cm in the greatest dimension .

In clinical evaluation, the actual size of the nodal mass should be measured, and allowance should be made for intervening soft tissues. Most masses larger than 3 centimeters in diameter are not single nodes but confluent nodes or tumors in soft tissues of the neck. There are 3 stages of clinically positive nodes: N1, N2, and N3. The use of subgroups a, b, and c is not required but recommended. Midline nodes are considered homolateral nodes.

Distant metastasis (M)

- MX - Distant metastasis cannot be assessed.
- M0 - No distant metastasis.
- M1 - Distant metastasis.

Grouping of Laryngeal cancer in stages

| | |
|-----------|--|
| Stage 0 | Tis N0 M0 |
| Stage I | T1 N0 M0 |
| Stage II | T2 N0 M0 |
| Stage III | T3 N0 M0, T1 N1 M0, T2 N1 M0, T3 N1 M0 |
| Stage IVA | T4 N0 M0, T4 N1 M0, any T, N2, M0 |
| Stage IVB | Any T, N3, M0; T4b, any N, M0 |
| Stage IVC | Any T, Any N, M1 |

Treatment

Supraglottic larynx is composed of multiple sites. Because all of the subsites are intimately related, and because the supraglottis is continuous with its neighboring hypopharynx, glottis larynx, and oropharynx, it can be difficult to determine the exact site of origin for many larger cancers. It is very important not only to cure the patient but also when it is possible to preserve the organ and all its function. The choice of treatment depends on the size (location), spread, growth form pattern (exophytic, endophytic), stage of the process, histological variant, patient's general state.

Early – stage primary disease is highly curable by partial laryngeal surgery or by radiation therapy. Patients with stage I – II laryngeal cancer are treated with radiation therapy alone. Surgical management (larynx resection) is employed in the case of recurrence after radiation therapy or if it failed.

Patients with stage I glottis cancer have risk of lymph node metastases – from 0% to 2 % for more advanced disease, stage II - 10%, stage III – 15%.

Patients with stage III – IV are recommended combined treatment preoperative radiation and surgery. Krail operation is employed in patients with metastases in lymph nodes. Subglottic region tumors are radoresistent, so surgery has been favored. Postoperative radiation follows operation.

Chemotherapy can be both combined with surgery and be employed alone in patients with gross infiltrative laryngeal tumors, metastases in remote organs recurrences and also when radical surgery is impossible. Chemotherapy can be combined with radiation therapy. Bleomycin, methotrexat, prospidin, vincristin, platidiam give good results in suppression of tumor growth.

Monochemotherapy

Prospidin. Radiation therapy follows monochemotherapy.

Polychemotherapy. The following drugs are used:

1. Bleomycin, cisplatin, methotrexat, vincristin. Courses are repeated after 4 weeks. Radial therapy follows polychemotherapy.
2. Methotrexat, bleomycin, prospidin. Two weeks later radiation therapy is recommended.
3. Fluorouracil, bleomycin, cisplatin. Courses are repeated after four weeks. Radiation therapy follows polychemotherapy.

Prognosis

Cure rates and survival rates can predict group outcomes, but can never precisely predict the outcome for a single individual. However, the earlier laryngeal cancer is discovered and treated, the more likely it will be cured.

Cancers found in stage 0 and stage 1 have a 75% to 95% cure rate depending on the site. Late stage cancers that have metastasized have a very poor survival rate, with intermediate stages falling somewhere in between. People who have had laryngeal cancer are at greatest risk for recurrence (having cancer come back), especially in the head and neck, during the first two to three years after treatment. Check-ups during the first year are needed every other month, and four times a year during the second year. It is rare for laryngeal cancer to recur after five years of being cancer-free.

Questions for self control

1. What causes laryngeal cancer?
2. Enumerate the symptoms related to laryngeal cancer.
3. What are the main methods of diagnosis?
4. What is the incidence rate of laryngeal cancer in Ukraine?
5. How is laryngeal cancer treated?

Tests (choose the correct option)

- 1. Mean age of laryngeal cancer incidence is:**
 - a) in the sixth decade;
 - b) in children;
 - c) young people;
 - d) teenagers.
- 2. Advanced laryngeal cancers are treated by**
 - a) surgery alone;
 - b) chemotherapy;
 - c) combination of radiation and surgery;
 - d) hormonotherapy.
- 3. Symptom characteristic for all localizations**
 - a) cough with sputum, sometimes bloody;
 - b) vomiting;
 - c) weight loss;
 - d) anorexia.
- 4. Risk factors for development of laryngeal cancer are**
 - a) Human papillomavirus;
 - b) alcohol consumption;
 - c) smoking;
 - d) exposure to ultraviolet radiation.
- 5. More than 95% of all primary laryngeal malignancies are:**
 - a) adenocarcinomas;
 - b) neuroendocrine tumors;
 - c) sarcomas;
 - d) squamous cell carcinomas.

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

ESOPHAGEAL CANCER

Incidence

Esophageal cancer (EC) (Fig. 5) is the 9th – 10th commonly diagnosed neoplasm.

In Ukraine the incidence of esophageal carcinoma was 4.1 persons per 100000 population in 2012 year (in men 7.8, in women 1.1 cases).

Esophageal cancer is more common in men. 80% of patients with EC are over 60. Middle Asia is the region with a very high incidence of EC.

Risk factors

- Age. Persons over 60.
- Sex. Cancer of the esophagus is more common in men than in women.
- Cigarette abuse or using smokeless tobacco is one of the major risk factors for esophageal cancer.
- Alcohol intake. Chronic and/or heavy use of alcohol is another major risk factor for esophageal cancer. People, who use both alcohol and tobacco, have an especially high risk of esophageal cancer.
- Any factor causing chronic irritation of the lining of esophagus.
- Obesity.
- Chronic esophagitis.
- Esophageal diverticula.
- Microtrauma of esophagitis (drinking of boiling hot tea, coffee and eating of very hot food).
- Esophageal achalasia.
- Gastroesophageal reflux
- Polyps

Esophageal cancer sites:

- Squamous cell carcinomas occur in the esophagus cervical 10% and in the upper 39% and middle thoracic 49% esophagus;
- Adenocarcinoma is usually located in the lower esophagus 2%.

Clinical presentation

I. Dysphagia of any stage. (Esophagus is narrowed to less than 13mm in diameter)

Ist. – Difficult swallowing of solid food.

IIst. - Difficult swallowing of porridge.

IIIst. – Difficult swallowing of liquid.

- Weight loss.



Fig. 5. Esophageal cancer

II. Advanced symptoms.

- Belch.
- Vomiting of just eaten food.
- Painful swallowing.
- Pain in the throat.
- Back pain.
- Pain behind the breastbone or between the shoulder blades.
- Salivation.
- Hoarseness or chronic cough.
- Hematemesis.
- Fetid smell.
- Feeling of food sticking in the epigastrium.
- Horner's syndrome (or paralysis of the recurrent laryngeal nerve).

Complications

- Esophagus perforation.
- Dislocation.
- Tumor overgrowth reflux structuring.
- Pressure necrosis.
- Bleeding from as the result of intubation.
- Aspiration.
- Pneumonia.
- Pleurisy.
- Cough from a tracheoesophageal fistula)

Diagnosing

Symptoms develop when the esophageal lumen is greatly narrowed and metastasis has occurred.

Basic methods

- History (anamnesis).
- Physical examination.
- Barium esophagogram.

A barium swallow is a series of X rays of the esophagus (Fig.6). The patient drinks liquid containing barium, which coats the inside of the esophagus. The barium shows any changes in the shape of esophagus.

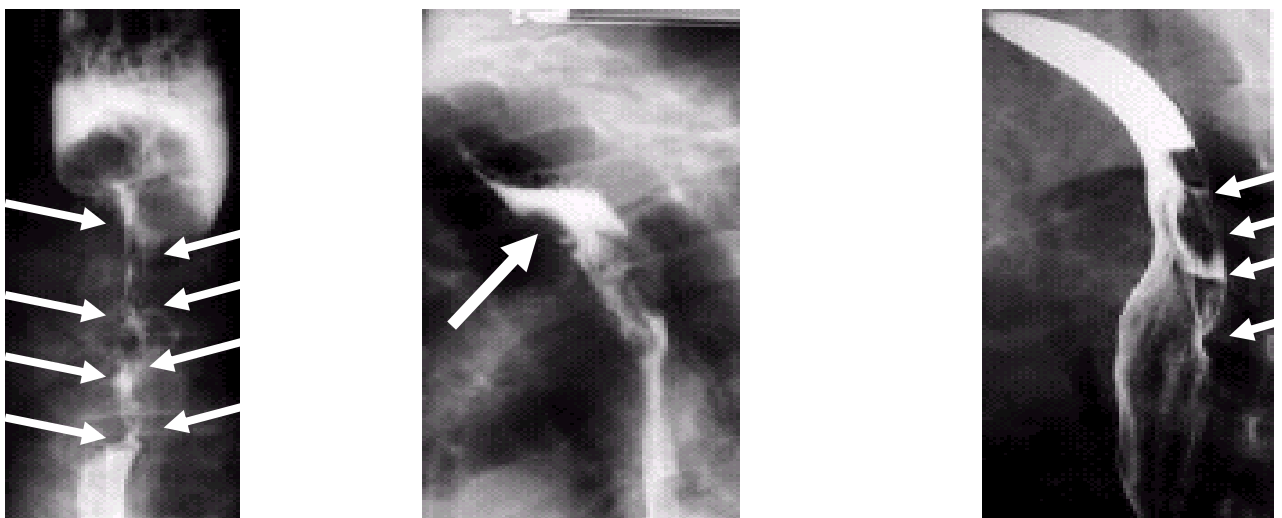


Fig. 6. Esophagus X – ray.

- Esophagoscopy (endoscopy) with biopsy.
- Biopsy can show cancer or tissue changes that may lead to cancer.
- Brushings of the tumor are diagnostic in 90% of cases.
- Computed tomography of the chest and abdomen.
- Abrasive cytology (uses a catheter and a balloon covered with cottonette to scrape loose esophageal mucosal cells). 90% accurate in patients with early cancer of the esophagus.

Histologic types of esophageal cancer

- Squamous cell carcinomas (fewer than 50% of EC).
- Adenocarcinomas, arising in Barrett's esophagus (50% of malignant lesions), and the incidence of this histology appears to be rising. Barrett's esophagus contains glandular epithelium cephalad to the esophagogastric junction.
- Gastrointestinal stromal tumors can occur in the esophagus and are usually benign.

Tumor location is: upper third in 25% of patients,
middle third in 52% of patients,
lower third in 23% of patients.

Classification of EC by TNM system

Primary tumor

- TX: Primary tumor cannot be assessed.
- T0: No evidence of primary tumor.
- Tis: Carcinoma in situ.
- T1: Tumor invades the lamina propria or submucosal.
- T2: Tumor invades the muscularis propria.
- T3: Tumor invades the adventitia.
- T4: Tumor invades adjacent structures.

Regional lymph nodes involvement:

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

Distant metastases involvement:

- MX: Distant metastasis cannot be assessed.
- M0: No distant metastasis.
- M1: Distant metastasis.

Grouping of EC in stages

Stage IA – T1N0M0

Stage IB – T2N0M0

Stage IIA – T3N0M0

Stage IIB – T1N1M0 or T2N1M0

Stage IIIA – T4aN0M0 or T3N1M0 or T1, T2 N2 M0

Stage IIIB – T3 N2M0

Stage IIIC – T4a N1M0 or T4a N2M0 or T4b Any N M0 or Any T N3 M0

Stage IV - Any T Any N M

Treatment

Surgical treatment

Surgery and radiation therapy are the main treatments of clinically localized esophageal cancer. Various techniques are used to resect the esophagus.

Types of resection

- It was Czerny, who operated the patient in 1877. This patient lived for 15 month.
- Torek performed the first successful trans – thoracic resection in 1913. The patient lived for 13 years. Patients with middle third EC undergo Dobromislov – Torek operation. Esophagus is resected through the left thoracotomy. The proximal cervical esophagus is brought out through an incision anterior to the sternocleidomastoid muscle and tunneled subcutaneously along the anterior chest wall, where a cutaneous esophagostomy is fashioned. The patient is fed via a rubber tube connecting the esophagostomy with a gastrostomy.
- Ohsawa, a Japanese surgeon from Kyoto reported his technique in 18 patients. It was the first successful resection of a thoracic esophageal cancer with reconstruction using the stomach. This operation is also called Ohsawa – Garlok operation.
- In 1946, Ivor Lewis (Fig. 7) proposed a combined laparotomy and right thoracotomy approach that provided excellent exposure for preparation of the conduit and for resection of the esophagus and reanastomosis of the conduit in the chest.

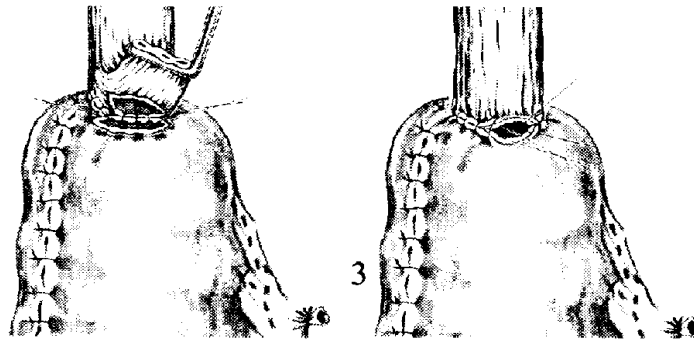


Fig. 7. Formation of anastomosis

Radiation therapy is used in treatment of carcinoma of the esophagus.

It is used:

- as a single modality, curatively or palliatively;
- combined with surgery, preoperatively or postoperatively;
- combined with chemotherapy;
- combined with chemotherapy and surgery.

Chemotherapy has been used to palliate patients with recurrence or metastases; as an adjuvant to surgery (preoperatively or postoperatively) in potentially curable patients; and with radiation therapy.

Aggressive multiagent therapy is not recommended for the patients with a poor performance status. Chemotherapy programs use singleagent and combination chemotherapy.

Prognosis

The 5-year survival rate:

I stage – 50 – 80%.

II stage – 35%.

III stage – 15%

Questions for self control

1. Name countries with the highest incidence of esophageal cancer.
2. What are the symptoms of esophageal cancer?
3. What causes esophageal cancer?
4. What are the main methods of diagnosis?
5. How is esophageal cancer treated?

Tests (choose the correct option)

- 1. Esophageal cancer is more common in**
 - a) Men;
 - b) Women;
 - c) Children;
 - d) Younger adults.
- 2. is the region with very high incidence of esophageal cancer.**
 - a) The USA.
 - b) Western Europe.
 - c) Australia.
 - d) Middle Asia.
- 3. The primary goal for patients with advanced local cancers or metastases is**
 - a) palliation;
 - b) surgery;
 - c) immunotherapy;
 - d) chemotherapy.
- 4. Most common symptoms of esophageal cancer are**
 - a) excruciating cough;
 - b) dysphagia;
 - c) loss of appetite;
 - d) thoracic mass.
- 5. was the first to successfully resect a cervical esophageal cancer.**
 - a) Torek;
 - b) Czerny;
 - c) Lewis;
 - d) Ohsawa.

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

GASTRIC CANCER

Incidence

The prevalence and death rates of gastric carcinoma (GC) have been markedly and significantly decreasing in all regions of the world and in all age groups by about 2 to 7% per year. Dietary factors and improvement in food storage are believed to be the major factors causing this decline. Improvements include reduction in toxic methods of food preservation (such as smoking and pickling), a decline in salt consumption, greater use of refrigeration, and increased consumption of fruits and vegetables. Mortality from gastric cancer is highest in East Asia (Hong Kong, Japan, and Singapore) and lowest in the United States. Of interest, the Nordic and Western European countries have incidence rates two to three times higher than the United States. The incidence remains high in Japan but decreases in the offspring of Japanese immigrants to the United States. The average age of onset is 55 years.

In Ukraine gastric cancer takes the third place in men and the fourth place in women among all oncology diseases. In Ukraine the incidence of gastric cancer is 22.9 per 100000 population in 2012 year (in men 29.4 in women 17.2 cases).

Risk factors

- Age (a peak incidence is in the 7th decade).
- Infection with *Helicobacter pylori* enhances the risk of gastric cancer.
- Diet. Daily intake of food with large concentration of nitrites, nitrates and salt, hot food, vitamin C deficiency, poor drinking water.
- Male sex (GC is twice as often in men than in women).
- Smoking.
- Menetrier's disease.
- Genetic factors (Napoleon, his father and grand father – all died from gastric cancer).
- Prior gastric surgery: resection of stomach and vagotomy.
- Gastritis – with impaired gastric acid secretion. (Nearly "0" index of acidity is obvious of cancer).
- Polyps: hyperplastic and adenomatous. Previous gastric surgery.
1 polyp – is 20% of transformation.

- 2 polyps – 60% of possibility.
- 3 polyps – 100% gastric cancer.
- Occupation (rubber, coal workers).

Anatomy

The stomach begins at the gastroesophageal junction and ends at the pylorus.

The stomach (Fig. 8) is a muscular organ that functions in storage and digestion. It has three parts and two sphincter mechanisms (gastroesophageal, pylorus). Stomach is divided into three parts – upper (C), medium (M), lower (A).

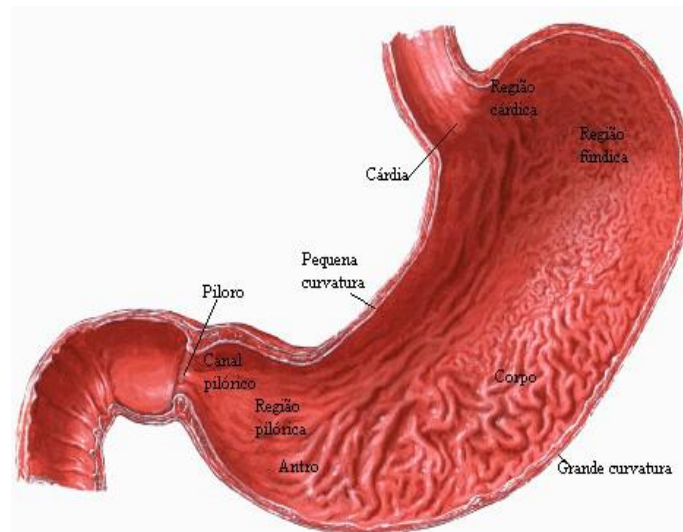


Fig. 8. Stomach anatomy.

Vasculature

Arterial supply to the stomach is via the right and left gastric arteries, the right and left gastroepiploic arteries, and the vasa brevia (Fig. 9).

1. **The right gastric artery** arises from the hepatic artery and supplies the lesser curvature.
2. **The left gastric artery** arises from the celiac axis and supplies the lesser curvature.
3. **The right gastroepiploic** originates from the gastroduodenal artery and supplies the greater curvature.
4. **The left gastroepiploic artery** branches from the splenic artery and supplies the greater curvature.

5. **The vasa brevia** the short gastric arteries arise from the splenic artery and make small contribution to the blood supply of the proximal portion of the stomach.

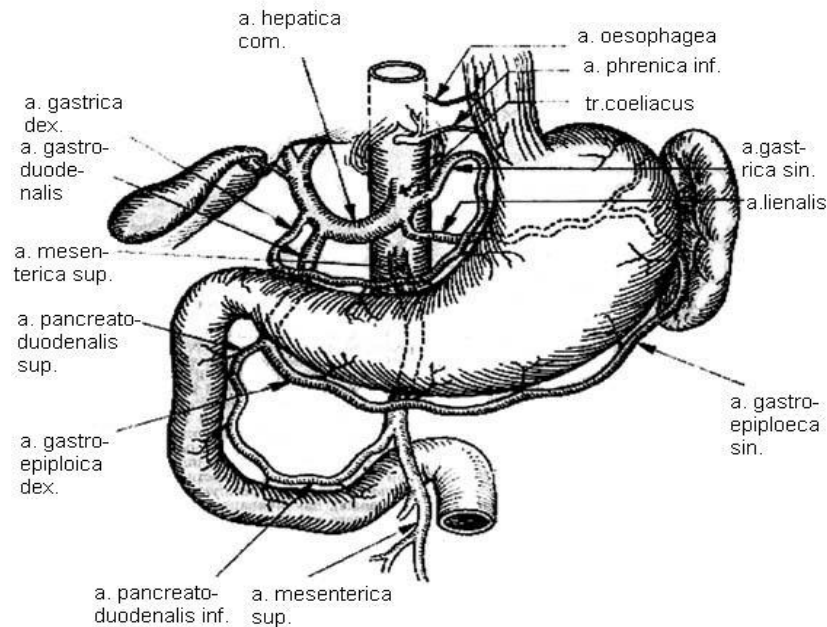


Fig. 9. Arterial supply to the stomach

Classification of gastric cancer by TNM system

Primary tumor

TX = primary tumor (T) cannot be assessed.

T0 = no evidence of primary tumor.

Tis = carcinoma in situ, intraepithelial tumor without invasion of lamina propria.

T1 = tumor invades lamina propria or submucosa.

T2 = tumor invades muscularis propria or subserosa.

T3 = tumor penetrates serosa (ie, visceral peritoneum) without invasion of adjacent structures.

T4 = tumor invades adjacent structures.

Regional lymph nodes

NX = regional lymph nodes (N) cannot be assessed.

N0 = no regional lymph node metastases.

N1 = metastasis in 1-6 regional lymph nodes.

N2 = metastasis in 7-15 regional lymph nodes.

N3 = metastasis in more than 15 regional lymph nodes.

Distant metastasis

MX = distant metastasis (M) cannot be assessed.

M0 = no distant metastasis.

M1 = distant metastasis.

Grouping of gastric cancer in stages

| | |
|-------------|--------------------------------------|
| Stage 0 | T _{is} No Mo |
| Stage I a | T ₁ No Mo |
| Stage I b | T ₁ N ₁ Mo |
| | T ₂ No Mo |
| Stage II | T ₁ N ₂ Mo |
| | T ₂ N ₁ Mo |
| | T ₃ No Mo |
| Stage III a | T ₂ N ₂ Mo |
| | T ₃ N ₁ Mo |
| | T ₄ No Mo |
| Stage III b | T ₃ N ₂ Mo |
| Stage IV | T ₄ N _{1,2,3} Mo |
| | T _{1,2,3} N ₃ Mo |
| | any T any N M ₁ |

Histological classification

1. Adenocarcinoma – is the most common form (95%)
 - papillary;
 - tubular;
 - mucous;
 - ring – form cell cancer.
2. Glandular – squamous cell carcinoma.
3. Squamous cell carcinoma.
4. Non – differentiated cancer.
5. Small – cell carcinoma.

Macroscopic forms

- Polypoid cancer (exophytic).
- Ulcerating lesions surrounded by elevated borders (exophytic).

- Ulcerated lesions infiltrating the gastric wall.
- Diffusely – infiltrating tumors.

There are five metastases of gastric cancer

- Virchow's metastasis of supraclavicular, on the left side.
- Sister Mary Joseph metastasis in the umbilicus.
- Krukenberg metastasis in ovary in women.
- Schnitzler's metastasis on peritoneum pouch of Douglas.
- Tumor invasion into stomach wall.

Clinical presentation

Early gastric cancer symptoms are not pathognomic. Early cancer is localized in mucous and submucous.

Due to the fact that both the stomach and abdominal cavity are large to distention, the symptoms of gastric cancer are obtained at an advanced stage.

Most patients with GC are diagnosed with advanced – stage disease.

In some patients, symptoms may suggest the presence of a lesion in specific locations. Dysphagia may indicate a tumor in the cardia with extension through the gastroesophageal junction. Early satiety is a symptom of GC (diffusely infiltrating tumor that has resulted in loss of distensibility of the gastric wall). Persistent vomiting is evidence of antral carcinoma obstructing the pylorus. Hematemesis occurs in 10% of GC patients.

Symptoms according to Savitsky

Local symptoms

- Pain in epigastria after food intake.
- Palpable tumor of epigastria.

Common symptoms

- Discomfort.
- Belching, early satiety.
- Stomach bloating.
- Fatigue.

- Anorexia (loss of appetite).
- Weight loss.

Complications

- Bleeding.
- Perforation.
- Growth into neighbouring/adjacent organs.
- Jaundice.

Diagnosis

- History (anamnesis).
- Physical examination.
- Endoscopic ultrasonography.
- Esophagogastroduodenoscopy with biopsy.
- Chest X-ray.
- Stomach X – ray and barium swallow.
- CT-scan of the abdomen.
- Laparoscopy.
- Diagnosis should be made on the basis of gastroscopic or surgical biopsy and histology given according to the WHO criteria.
- Palpation per. Rectum – Shnitsler metastasis.

The results of biopsy

- Pseudo negative.
- Pseudo positive.

Staging and risk assessment

Stages predict survival. Primary tumor stage is based on the depth of invasion and the presence and extent of serosal invasion. The stage is defined according to the TNM system.

Treatment

Surgery

Surgery is the most common curative modality for localized gastric cancer treatment.

- Resection is recommended for stages Tis-T3N0-N2M0 or T4N0M0.
- Patients with gastric cancer undergo different types of resection. The choice of gastric resection depends upon the location of the tumor, its histologic type and the stage of the disease. The types of resection are: gastrectomy, distal subtotal gastrectomy, proximal subtotal gastrectomy.

Radiation and chemotherapy

Radiation and chemotherapeutic modalities can be used for palliation or as adjuvant therapy.

Radiation therapy alone is adjuvant to surgical resection of gastric cancer. Radiation therapy as an adjuvant have used concomitant 5 – FU chemotherapy. Now most effective and safe medicamental form of 5 – FU, Adriamycin, and mitomycin – C (FAM).

Different combinations of chemotherapy with irradiation have been used. But advantage has been shown for drug regimen 5 – FU chemotherapy.

Prognosis:

Lymphatic invasion occurs early. 50% of patients have lymphatic disease at the time of resection. The percentage of patients who are cured after surgical therapy is low.

- Most patients are diagnosed at an advanced stage, and even after curative gastrectomy, locoregional and distant disease recurs in 80% of patients.
- Prognosis depends on the depth of gastric wall invasion involvement of regional nodes and the presence of distant metastases.
- The 5 year survival rate for curative surgical resection ranges from 30-65% for patients with stage II disease, and from 10-35% for patients with stage III disease.

Questions for self control

1. Define gastric cancer and explain the causes of this disease.
2. What are the symptoms of gastric cancer?
3. What do you know about metastases of gastric cancer?
4. Give gastric cancer classification.
5. What complications are typical of gastric cancer?

Tests (choose the correct option)

- 1. Which modality is the most common for localized gastric cancer treatment?**
 - a) radiation therapy for palliation;
 - b) adjuvant chemotherapy;
 - c) surgery;
 - d) combined surgery, radiation and chemotherapy.
- 2. Early satiety is a symptom of:**
 - a) larynx cancer;
 - b) gastric cancer;
 - c) pancreatic cancer;
 - d) liver cancer.
- 3. is the most common curative modality for localized gastric cancer treatment.**
 - a) Radiation therapy;
 - b) Chemotherapy;
 - c) Surgery;
 - d) Combination of chemotherapy and radiation therapy.
- 4. The optimal method of gastric cancer diagnosis is**
 - a) CT;
 - b) MRI;
 - c) endoscopy with biopsy;
 - d) gastric cancer X – ray.
- 5. The most common histologic type of stomach cancer is**
 - a) small – cell carcinoma;
 - b) squamous cell carcinoma;
 - c) adenocarcinoma;
 - d) sarcoma.

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

LIVER CANCER

Incidence

Liver cancer (LC) is one of the most common malignancies and the most common cause of cancer deaths in the world. One million deaths due to hepatocellular carcinoma (HCC) occur each year worldwide. It ranked 5th among all malignant neoplasms in 2005 year. The annual incidence of new liver cancers cases is 16.000 in the USA. Primary liver cancer (PLC) constitutes 2.5% of all malignant tumors in Europe and North America, 16 – 19% in the countries of the South – East Asia and 50% in some regions of South Africa. The incidence of liver cancer is 6 persons per 100000 population in 2012 year in Ukraine.

Risk factors

Conditions predisposing to HCC

- 1. Hepatitis B virus (HBV).** Chronic infection on the basis of cirrhosis increase the risk of HCC by 1000 – fold. This is the most common cause worldwide.
- 2. Cirrhosis.** HCC very often develops in a cirrhotic liver. In France, the development of HCC in the presence of alcoholic cirrhosis was nearly always associated with HBV infection, and alcoholism was thought to hasten the development of HCC. In Italy, the prevalence of HCC in individuals with cirrhosis was nearly 7 percent with a yearly crude incidence of 3 percent; hepatitis C virus chronic infection was the cause of cirrhosis in 45 percent of these patients.
- 3. Hepatitis C virus (HCV)** infection is a risk factor for the development of HCC. Apparently HCV induces cirrhosis and to a lesser extent increases the risks for patients with cirrhosis. HCV infection acts independently of HBV infection, alcohol abuse, age, and gender. The ratios for HCC risk factors in patients with chronic liver disease, adjusted for age, sex, and other factors.
- 4. Aflatoxin.** Aflatoxin has been proven to be a potent hepatocarcinogen. This byproduct of fungal contamination of foodstuffs in Africa and the Philippines causes DNA damage and mutations of the p53 gene. For example, the daily intake of aflatoxin in Mozambique is

four times greater than in Kenya, and the incidence of HCC is eight times greater.

6. Sex hormones. The risk for liver cell adenomas and HCC is increased in women who have used oral contraceptives for eight or more years.

7. Cigarette smoking, alcohol intake, diabetes, and insulin intake. 50% of alcoholics may have sub – clinical HCC at autopsy. The risk of HCC increases if the patient gives up drinking alcohol because heavy drinkers do not survive long enough to develop cancer.

8. Other factors. A relatively small number of HCCs develop in patients with various other diseases. The most common of these are α_1 -antitrypsin deficiency, tyrosinemia, and hemochromatosis. Phlebotomy therapy can deplete hepatic iron and induce regression of hepatic fibrosis but does not prevent the development of HCC in hemochromatosis. Clonorchiasis, vinyl chloride exposure, and administration of thorium dioxide or methotrexate are also associated with the development of HCC.

Pathology

Hepatobiliary system tumors can be benign or malignant and by the tissue of origin, whether the mesenchymal or epithelial neoplasms. Malignant epithelial neoplasms constitute about 90% of all liver tumors. 10% are benign, usually of epithelial origin.

Mixed HCC/cholangiocarcinoma constitutes 1% of liver tumors. Malignant mesenchymal tumors constitute about 2%.

1. Liver cell adenoma (Fig. 10) has low malignant potential. Liver adenomas are rare and occur mostly in women taking oral contraceptives. The majority of adenomas are solitary; occasionally multiple tumors develop in patients with liver cell adenomatosis. These tumors are smooth encapsulated masses and do not contain Kupffer cells. Patients are usually symptomatic; hemoperitoneum occurs in 25% of cases.



Fig.10. Liver cancer

2. Focal nodular hyperplasia (FNH) has no malignant potential. FNH occurs in female twice more often than in male. Only one-half of patients with FNH have taken oral contraceptives. FNH tumors are nodular, without capsule, but they contain Kupffer cells. Patients are usually asymptomatic; hemoperitoneum rarely occurs.

3. HCC may have massive, nodular, and diffuse forms. The growth pattern microscopically is trabecular, solid, or tubular, and the stroma, in contrast to the bile duct carcinoma, is scanty. Because of hypercalcemia it has sclerosing or fibrosing form. Fibrolamellar carcinoma occurs predominantly in young patients without cirrhosis, has a favorable prognosis, and has no elevation of serum alpha fetoprotein levels. In the United States almost half of HCCs in patients under 35 years of age are fibrolamellar, and over half of them are resectable.

4. Bile duct adenomas are solitary (80%) and resemble metastatic carcinoma. Most are less than 1 cm in diameter and encapsulated.

5. Biliary cystadenoma and cystadenocarcinoma. Benign and malignant cystic tumors of biliary origin arise in the liver more frequently than in the extrahepatic biliary system.

6. Bile duct carcinoma (cholangiocarcinoma). Malignant tumors of intrahepatic bile ducts are less common than HCC and have no relation to cirrhosis. Mixed hepatic tumors with elements of both HCC and cholangiocarcinoma do occur; the majority of these cases are actually HCC with focal ductal differentiation.

Histologic findings. Histology is quite variable, ranging from well – differentiated tumors to anaplastic ones.

Classification of hepatic cancer by TNM system

Primary tumor (T)

T1 – Solitary tumor smaller than or equal to 2 cm, no vascular invasion

T2 - Solitary tumor smaller than or equal to 2 cm, with vascular invasion:

- Multiple tumors, in 1 lobe only, smaller than or equal to 2 cm, No vascular invasion.
- Solitary tumors larger than 2 cm, no vascular invasion
- T3 - Solitary tumors larger than 2 cm, no vascular invasion.
- Multiple tumors, in 1 lobe only, with vascular invasion.
- T4 - Multiple tumors involving more than 1 lobe.
- Involvement of a major branch of the portal or hepatic vein.

Regional lymph nodes (N)

N0 – Indicates no nodal involvement.

N1 – indicates regional nodal involvement.

Distant Metastasis (M)

M0 – Indicates no distant metastasis.

M1 – Indicates metastasis presence beyond the liver.

Grouping of hepatic cancer in stages

Stage I – T1N0M0

Stage II – T2N0M0

Stage IIIA – T3N0M0

Stage IIIB – T1-3N1M0

Stage IVa – T4N0M0

Stage IVB – Any T any N M1

Clinical presentation

Common symptoms:

Weight loss – 35%.

Abdominal pain – 91%.

Weakness 31%.

Jaundice – 7%.

Vomiting 8%.

Stoutness and anorexia – 27%.

Abdominal swelling (43%).

Common signs:

Jaundice - 41%.

Fever - 38%.

Splenomegaly - 65%.

Hepatomegaly - 89%.

Hepatic bruit - 28%.

Ascites - 52%.

Muscle wasting.

Bone pain may occur in 3 to 12% of patients, but necroses indicates pathologic bone metastases.

Weight loss in cirrhotic patient indicates developing HCC.

Abdominal swelling can be the result of ascites or rapidly expanding tumor.

Diagnosis

1. **History** (a past history of hepatitis or jaundice, blood transfusion, use of intravenous, drugs, sex hormones).
2. **Physical examination** (assessment of hepatic size presence of masses, tenderness).
3. **α - fetoprotein (AFP)** is an oncomarker. The concentration of AFP over 20 mg/l is obvious of HCC. The higher AFP level the bigger hepatic neoplastic mass.
4. **Biopsy of liver nodules.** Some authors believe that percutaneous liver biopsy carries a high risk and has little or no role in the workup of liver tumors, while others believe that it can be performed without any significant risk. Nevertheless, liver biopsy is necessary to establish the diagnosis and may be obtained either at operation or percutaneously. Core liver biopsy of the mass is performed under ultrasound or CT guidance.
5. **Lab studies.** Alpha – fetoprotein (AFP) is elevated in 75% of cases. The level of elevation correlates inversely with prognosis. An elevation of greater than 400 ng/ml predicts HCC with specificity greater than 95%.
6. **Radiologic studies**
 - a. **Ultrasound.** US imaging of HCC is variable. Metastatic deposits are usually hyperechogenic but may be hypoechogenic.

- b. Abdominal CT scan.** Proper technical performance of CT with imaging in the hepatic – arterial and portal – venous phases, as well as delayed – contrast images, is important in detecting HCC.
- c. MRI.** HCC imaging varies on MRI depending on multiple factors, such as hemorrhage, degree of fibrosis, histological pattern, degree of necrosis, and the amount of fatty change. MRI can help differentiate cirrhotic well by MRI.
- d. Angiography.** This method of diagnosis can confirm portal vein involvement, define the arterial supply, and identify vascular lesions that are as small as 3 mm in diameter. Intra-arterial epinephrine injection can differentiate normal hepatic artery, and portal veins or hepatic veins invasion may be present.

5. Radionuclide scans

Liver-spleen scan. Sulfur – colloid study typically demonstrates an area of decreased labeling in HCC. A "cold" defect in the liver with signs of cirrhosis strongly suggests HCC.

Liver gallium scan can differentiate primary hepatic tumors from metastatic carcinoma because gallium is taken up by the HCC. On gallium scan, up to 90% of HCCs demonstrate uptake of radiopharmaceutical drug. Gallium may help distinguish regenerating nodules of cirrhosis from HCC since regenerating nodules typically do not label with gallium.

Treatment

80% - 90% of the liver can be removed during surgical resection with lobectomy or with segmentectomies wedge resection of individual lesions. Early identification and ligation of structures within the porta hepatic coursing to the lobe to be resected is very important. Recently preoperative roentgenendovascular occlusion both of hepatic artery or its branches and branches of hepatic portal is made.

Occlusion of hepatic portal and arterial inflow can be obtained by Pringle maneuver by encircling the structures of the porta hepatis with clamp.

This maneuver can be performed 45 to 60 minutes during the course of hepatic resection and decreases blood loss greatly.

Patients with advanced bilobar HCC or with HCC in the presence of advanced cirrhosis are managed by liver transplantation.

Treatment of nonresectable and metastatic disease.

Unresectable Hepatocellular carcinoma has been treated by ultrasound – guided ethanol injections and arterial or endoscopic embolization.

Palliation by decreasing the size of tumor is managed by systemic and regional chemotherapy, tumor destruction by ethanol injections or cryodestruction. Treatment of patients with single or in combination with other drugs (5 – fluorouracil, doxorubicin and mitomycin) in a systemic way is not efficient.

Regional chemotherapy is more effective. It is managed by so – called intervention radiological methods. They are: chemoinfusion in hepatic artery (CIHA), chemoembolization of hepatic artery (CEMA) and portal vein (CEPV).

Chemoembolization combines regional chemotherapy and local asphyxia of tumor.

Chemoembolization of hepatic artery is performed with cytostatic suspension in oil contrast substance (iodized oil) with occlusion of hepatic artery by pieces of hemostatic sponges. Embolization is toxic. 1/3 of patients have postembolization syndrome, presence of abdominal pain, high fever, vomiting, anorexia, stomach paresis, cystic artery spasm.

Cryosurgery of liver malignant tumors can prolong survival in patients with primary liver cancer. Liquid nitrogen freezing can be monitored by ultrasonic probe. Cryosurgery is very effective and is indicated to the patients with multiple bilobar tumors less than 5 cm and tumors closely adjacent to arteries, when operation is risky.

Tumor node destruction is performed by 96% ethyl alcohol injection into tumor node under ultrasound – guidance.

Prognosis

There are many negative factors influencing the survival of the HCC patients. They are: lymph node involvement, vascular invasion, diffuse spreading type of HCC, absence of the capsule, tumors larger than 5 cm, multiple or bilobar tumors. Unresectable hepatocellular carcinoma

prognosis is very poor. Median survival for nontreated patients is 13 months.

Survival rates after transplantation and resection for stages III and IV of HCC are poor: 20% survival after 2 years. 5 year survival after radical resections is 10% – 17%.

3 year survival for TNM stage II – 75%

TNM stage III – 50%

TNM stage IVA (nonmetastatic) – 10% - 20%.

Survival is better in absence of cirrhosis.

Questions for self control

1. Primary and metastatic hepatic cancer.
2. What are clinical symptoms of HCC?
3. What diagnostic methods are used for liver neoplasms detection?
4. What are risk factors of HCC?
5. What types of resection are used?
6. Growth patterns and histology.

Tests (choose the correct option)

- 1. The common causes of HCC are**
 - a) hepatitis B;
 - b) hepatitis C;
 - c) cirrhosis;
 - d) all above mentioned.
- 2. The most common HCC symptom is**
 - a) vomiting;
 - b) anorexia;
 - c) abdominal pain;
 - d) leg pain.
- 3. The most common primary malignant hepatic tumor is**
 - a) squamous cell carcinoma;
 - b) hepatocellular carcinoma;
 - c) basal cell carcinoma;
 - d) cholangiocellular carcinoma.
- 4. of the liver can be removed by surgical resection**
 - a) 15%;
 - b) 5%;
 - c) 35-40%;
 - d) 80 – 90%.
- 5. 5 year survival after radical resection is**
 - a) 75%;
 - b) 10 – 17%;
 - c) 50%;
 - d) 20%.

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

PANCREATIC CANCER

Incidence

Pancreatic cancer (PC) ranks 13th in the incidence and the 8th as a cause of cancer death in the world. Mortality to morbidity ratio is 0.99. The incidence of PC in industrial countries is very high and it is low in India, Vietnam, South America. In Ukraine the incidence of pancreatic cancer is 11.0 per 100000 population in 2012 year (in men 12.8, in women 9.5 cases).

Risk factors

The cause of pancreatic cancer remains unknown but several factors are associated with its occurrence.

- **Cigarette smoking.** Cigarette smoke contains carcinogens, including nitrosamines that have induced pancreatic malignancies in laboratory animals.
- **Dietary factors:**
 - coffee intake (is not confirmed);
 - alcohol consumption (is not confirmed);
 - meat intake;
 - fat.
- **Industrial chemicals.**
Long – term exposure to solvent and petroleum compounds, benzidine, β - naphthylamine, nitrosamines, azaserine, metal dust.
- **Cholecystokinin** is the primary hormone that causes growth of exocrine pancreatic cells; others include epidermal growth factor and insulin – like growth factors. Pancreatic cancer has been induced experimentally by long-term duodenogastric reflux, which is associated with increased cholecystokinin levels. Some clinical evidence suggests that cholecystectomy, which also increases the circulating cholecystokinin, may increase the risk of pancreatic cancer.
- **Genetic factors.**
- **Diabetes mellitus.**
- **Chronic and hereditary pancreatitis** is associated with pancreatic cancer. Chronic pancreatitis is associated with a 15 – fold increase in the risk for pancreatic cancer

- **Gastrectomy.**
- **Stomach resection.**

Classification of pancreatic cancer by TNM system

Primary tumor (T)

- Tx – Primary tumor cannot be assessed.
- T0 – N0 evidence of primary tumor.
- Tis – Carcinoma in situ.
- T1 – Tumor limited to the pancreas, 2 cm or smaller in the greatest dimension.
- T2 – Tumor limited to the pancreas, larger than 2 cm in the greatest dimension.
- T3 – Tumor extension beyond the pancreas but not involving the celiac axis or superior mesenteric artery.
- T4 – Tumor involves the celiac axis or superior mesenteric arteries.

Regional lymph nodes (N)

- Nx – Regional lymph nodes cannot be assessed.
- N0 – No regional lymph node metastasis.
- N1 - Regional lymph node metastasis.

Distant Metastasis (M)

- M0 – No distant metastasis.
- M1 – Distant metastasis.

Grouping of regional lymph node metastasis in stages

- Stage Ia T1N0M0
- Stage Ib T2N0M0
- Stage IIa – T3N0M0
- Stage IIb – T1-3N1M0
- Stage III – T4 Any N M0

Pathology

Pancreatic tumors arise from the endocrine and exocrine parenchyma of the gland. 95% of tumors are of exocrine origin, 5% are endocrineones.

Ductal adenocarcinoma is the most common pancreatic malignant tumor, it accounts for 80% of all pancreatic cancers. Median tumor size at diagnosis is 5 cm. Median survival is 16 weeks. 1 year survival is 17% of patients, 5 year survival is 1%.

Giant cell adenocarcinoma (looks like hemorrhagic cyst) is in 6% of patients. At diagnosis they are often large – up to 11 cm. Median survival is 8 weeks. No patient has lived more than 1 year.

Glandular – squamous cell carcinoma accounts for 4% of all tumors. In men it develops 3 times more often than in women. Cancer is diagnosed in tail rarely, 60% of all tumors are in the pancreatic head. Median survival is 24 weeks. This type of carcinoma may be multilocular. 1 year survival in 1% of patients. 5 year survival 0%.

Mucous adenocarcinoma accounts for 2% of all pancreatic tumors. 78% of tumors are localized in the pancreatic head, 22% in other parts of the pancreatic body. Median tumor size is 6 cm at first diagnosis. Median survival is 44 weeks. 1 year survival in 33%.

Mucous cystadenocarcinoma accounts for 1% of all PC. It is usually seen in women. 60% of tumors are localized in the pancreas body, 20% in the pancreatic head, and 20% in the pancreatic tail. Some tumors are very large - up to 16cm at the first diagnosis. 50% of patients can be cured with surgery alone (5 year survival). Unlike benign cysts they have walls and septa.

Acinar cell carcinoma is very rare – 1%. It occurs more often in men. Tumors in the head of the pancreas constitute 43% and in the pancreatic body – 43%. Median tumor size at diagnosis is 5 cm. Median survival is 28 weeks. 1 year survival is 14%. 5 year survival is 0%.

Clinical presentation

The disease is difficult to diagnose in its early stages, and most patients have incurable disease by the time they present with symptoms.

Early PC symptoms are:

- Visceral afferent nerves obstruction;
- Epigastric distention;
- Ascites;
- Fatigue;
- Constipation.

The initial symptoms are nonspecific, that's why early diagnosis of PC is difficult. A delay in diagnosis of some months from the initiation of symptoms is common.

- Diabetes mellitus is a sign of PC development.
- Obstructive jaundice occurs in 90% of PC patients and is a sign of pancreatic head lesions. Painless jaundice is not common in pancreatic carcinoma. Jaundice symptoms are: dark urine, pale stools and itch. 29% of patients have a palpable gallbladder at presentation (Courvoisier symptom). Jaundice occurs in 7% of patients with lesions of pancreatic body. Jaundice in lesions is conditioned by metastases to the liver.
- Pain is the most common symptom in patients with pancreatic cancer. Almost all patients have pain at some moment in the course of their disease. The pain in the epigastrium is often called "gnawing" and may be relieved with meals (as it usually happens with peptic ulcer disease). Severe pain is characteristic of the pancreatic body and tail. Radiation of pain to the thoracic or lumbar back occurs in many patients. Severe pain can indicate local tumor infiltration into the retroperitoneum and splanchnic nerve plexus and is usually considered a sign of unresectability.
- Weight loss even in the absence of loss of appetite is a common symptom. The cause of weight loss is not clear.
- Anorexia occurs in 64% of PC patients. Vomiting and nausea are seen in 43% to 45%. Duodenal and stomach obstruction as the result of local tumor invasion can be the cause of anorexia.
- Abdominal distention with ascites in the umbilicus region, splenomegaly (occurs in the result of vena porta or splenic vein obstruction) are seen in some patients at diagnosis. Metastases in the peritoneum can be caused by intestine obstruction, venous thrombosis and thrombophlebitis.
- depression (67%);
- dyspnea, dizziness or edema (20%);
- hoarseness (25%);
- taste change (25%);
- cough (10%);
- diarrhea (fat malabsorption) 10%;
- itching (10%);
- dysphagia (5%).

Diagnosis

Clinical findings

At presentation patients with pancreatic cancer have:

- cachexia (44%),
- palpable abdominal mass (35%),
- serum albumin concentration less than 3.5 g/dl (33%),
- ascites (25%),
- or jaundice (20%).

Metastases are present to at least one major organ in 65 % of patients, to the liver in 45 %, to the lungs in 30 %, and to the bones in 3 %. Carcinomas of the distal pancreas do not produce jaundice until they metastasize and may remain painless until the disease is advanced. Occasionally, acute pancreatitis is the first manifestation of pancreatic cancer.

Paraneoplastic syndromes

Release of lipase from the tumor, Panniculitis-arthritis-eosinophilia, dermatomyositis, polymyositis, recurrent, idiopathic deep vein thrombosis, and Cushing's syndrome are associated with pancreatic cancer.

Methods of diagnosis:

- 1. Ultrasonography (US).** Abdominal US is technically adequate in 60 to 90% of patients, is noninvasive, safe, and inexpensive. US can detect pancreatic masses as small as 2 cm, dilatation of the pancreatic and bile ducts, hepatic metastases, and extrapancreatic spread. Intraoperative US facilitates surgical biopsy and may detect unsuspected metastases in 50% of patients.
- 2. CT** is preferable to US because it can also demonstrate retroperitoneal invasion and lymphadenopathy, both of which are not well detected by US. A pancreatic tumor of 2 cm and more in diameter becomes visible. "Dynamic CT" with continuous infusion of intravenous contrast is the best test for assessing the size of the tumor and its extension. At least 20 % of pancreatic tumors believed to be resectable may not be detected by CT.

3. MRI has no noticeable advantage over CT in the diagnosis and staging of pancreatic cancer. MRI is used for imaging the biliary tree and pancreatic duct in patients with jaundice.

4. Endoscopic retrograde cholangiography (ERCP) is highly sensitive in detecting pancreatic carcinoma. 90% - 95% of patients with pancreatic adenocarcinoma have abnormalities on ERCP findings.

It may be difficult to distinguish between pancreatic cancer and chronic pancreatitis because both diseases share clinical and radiologic characteristics. Pancreatic duct stricture usually does not exceed 5 mm in chronic pancreatitis; strictures longer than 10 mm (especially irregular) indicate pancreatic cancer. Cytologic examination of cells in samples of pancreatic juice obtained during ERCP with secretin stimulation has been reported to be highly specific for the diagnosis of carcinoma and 85% sensitive. Brush biopsy of the pancreatic stricture (when possible) increases the diagnostic yield.

5. Percutaneous fine-needle aspiration cytology is safe and reliable, with a reported sensitivity of 55 to 95% and no false-positive results for the diagnosis of pancreatic cancer. This procedure should be performed for histologic confirmation on all patients with unresectable or metastatic disease unless a palliative surgical procedure is planned. Needle aspiration cytology distinguishes adenocarcinoma from islet cell tumors, lymphomas, and cystic neoplasms of the pancreas that are less aggressive and do not have a cystic appearance on CT or ultrasound.

The drawbacks to percutaneous aspiration biopsy include the potential tumor seeding along the needle tract, an increase in intraperitoneal spread, and a negative biopsy result that does not exclude the diagnosis of malignancy. Early and smaller tumors are usually missed by this technique.

6. Angiography is excellent for assessing major vascular involvement but is not very useful in determining the size and location of tumor (pancreatic cancer is hypovascular).

7. Laparoscopy can demonstrate extrapancreatic involvement in 40% of patients without demonstrable lesions on CT.

8. Tumor markers. No currently used serum marker is sufficiently sensitive or specific to be considered reliable for screening of pancreatic cancer.

- a. **CA 19-9** is carbohydrate antigen 19-9 (CA 19-9). It is widely used for the diagnosis and follow-up of patients with pancreatic cancer. The reference range of CA 19-9 is less than 33 – 37 U/ml. In the absence of biliary obstruction or benign pancreatic disease, a CA 19-9 value greater than 100 U/ml is highly specific for malignancy, usually pancreatic one. Fewer than 4% of patients with a CA 19-9 level of more than 300 U/ml have been found to have resectable tumors.
- b. **CEA** (Carcinoembryonic antigen) is of minimal value in diagnosis of pancreatic cancer. Only 40 – 45% of patients with pancreatic carcinoma have elevations in CEA levels. Multiple other benign and malignant conditions can lead to elevated CEA levels; thus, CEA is not a sensitive or specific marker for pancreatic cancer.

Many other tumor markers have been studied in pancreatic cancer, but none has yet been shown to general clinical utility in this disorder. All of the above mentioned imaging studies may show abnormalities that may not help to differentiate between pancreatic carcinoma and chronic pancreatitis. Even tumor markers can be elevated in patients with chronic pancreatitis. In these patients it is recommended to combine studies, to diagnose an underlying pancreatic carcinoma.

Treatment

Surgery

It is universally recognized that surgery is the primary therapy of treatment for pancreatic cancer. It increases survival of patients with pancreatic cancer after surgical resection.

Only 5% to 20% of patients with pancreatic cancer have resectable tumors at the time of presentation. The remaining require some form of palliation for the relief of jaundice, duodenal obstruction, or pain.

Tumors are resectable if:

- there are no metastases outside the abdomen;
- the tumor has not involved the portal hepatis, and the portal vein as it passes behind the body of pancreas, and the superior mesenteric artery region;
- the tumor has not spread to the liver or other peritoneal structures.

1) *Pancreaticoduodenectomy*, the Whipple's procedure, is the standard operation for carcinoma of the pancreatic head. This operation involves en bloc resection of the pancreatic head; the first, second, and third

portions of the duodenum; the distal antrum; and the distal common bile duct.

The gastrointestinal tract is then reconstructed with creation of a gastrojejunostomy, choledochojejunostomy, and pancreaticojejunostomy.

- 2) *Distal pancreatectomy*, usually with splenectomy and lymphadenectomy, is the procedure performed for carcinoma of the midbody and pancreatic tail.
- 3) *Total pancreatectomy* has been proposed for the treatment of pancreatic cancer. The procedure has two potential advantages:
 - removal of a possible multicentric tumor (present in up to 40% patients);
 - avoidance of a possible multicentric tumor (present in up to 40% of patients);
 - avoidance of pancreatic duct anastomotic leaks.
- 4) *Palliative procedures* are performed more frequently, because many tumors are incurable.
 - gastrojejunostomy with choledochojejunostomy;
 - percutaneous transhepatic biliary stents.

Chemotherapy

The most active single agents for pancreatic cancer have been 5 – fluorouracil (5 – FU) and capecitabine (Xeloda). Xeloda appears to be slightly more active than 5 – FU.

Combination chemotherapy regimens that include 5 – fluorouracil (5 – FU) have produced a response (temporary tumor regression or, rarely, cure) in about 20% - 25% of patients with metastases.

Radiation therapy (RT)

RT alone has little impact on pancreatic carcinoma. Radiation therapy in combination with surgical resection has been used to improve local control and survival. Moderate dose preoperative radiation therapy may increase resectability and survival. Radiation therapy is the main treatment for patient with locally advanced disease.

Prognostic factors

Performance status and some symptoms (dyspnea, anorexia, weight loss, and xerostomia) influence survival.

20% of the patients survive in the first year, 3% are alive 5 years after the diagnosis.

1 year survival < 20% of patients with adenocarcinoma of the pancreas;

5 year survival < 3% of patients with adenocarcinoma of the pancreas;

5 year survival of the patients after resection is up to 25%;

5 year survival of the patients after resection of small tumor (2cm) – 30%;

5 year survival of the patients without lymph node metastasis is 55%;

The mean survival for patients with unresectable disease is 3 – 6 months.

Questions for self control

1. Describe incidence, major causes of pancreatic cancer.
2. What growth patterns are known?
3. Describe clinical symptoms of pancreatic cancer.
4. Methods of pancreatic cancer diagnoses.
5. What kind of surgical operations are used for pancreatic cancer treatment?

Tests (choose the correct option)

1. 80% of all pancreatic cancers are

- a) papillary cystic carcinoma;
- b) adeno – squamous carcinoma;
- c) giant – cell carcinoma;
- d) adenocarcinoma.

2. of Pancreatic tumors are of exocrine origin

- a) 15%;
- b) 45 – 70%;
- c) 95%;
- d) 5%.

3. Tumor marker for pancreatic cancer is

- a) AFP;
- b) CA 19 – 9;
- c) PSA;
- d) CA 125.

4. Early PC symptoms are

- a) bleeding;
- b) painless obstructive jaundice;
- c) constipation;
- d) dysphagia.

5. The primary therapy for PC is

- a) hormonotherapy;
- b) chemotherapy;
- c) radiotherapy;
- d) surgery.

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

COLORECTAL CANCER

The large bowel is divided into the colon and rectum. Colon is a part of digestive system. Esophagus, stomach, small and large intestine are constituents of the digestive system. The last 6 inches of the large intestine are rectum, which ends in anal canal. The first 6 feet are colon.

Colorectal cancers are:

- cancer of the cecum;
- cancer of the ascending colon;
- cancer of the transverse colon;
- cancer of the descending colon;
- cancer of the sigmoid colon;
- cancer of the recto – sigmoid corner of the rectum;
- cancer of the ampulae of rectum.

Rectal cancer is the cancer of the anal canal of the rectum.

Epidemiology

Incidence

Worldwide the incidence rates of colorectal cancer (CC) differ. The incidence is the highest in civilised highly – developed countries (USA, Canada, Western Europe). Colon to rectal cancer ratio is 2:1 in developed countries and 1:1 in the rest ones. In Ukraine the incidence of colorectal cancer was in 2012 year 29.5 persons per 100000 population (in men 22.5, in women 22.6 cases).

The most common sites of CC spread are:

- cecum and ascending colon – 27%;
- transverse colon – 10%;
- descending and sigmoid colon – 36%;
- rectum sites – 8%.

Risk factors

Certain factors increase a person's risk of developing the disease.

- Age. The risk of developing colorectal cancer increases with age. Most cases develop at age of 64 years.

Precancerous disease.

- Polyps of the colon, particularly adenomatous polyps. The evolution to cancer is a multistage process that proceeds through mucosal cell

hyperplasia, adenoma formation and growth and dysplasia, to malignant transformation and invasive cancer.

- Patients who have previously been diagnosed and treated for colon cancer.
- Women, who have had cancer of the ovary, uterus, or breast.
- Genetic factors. Familial adenomatous polyposis syndrome, familial diffuse polyposis Peutz – Jeghers syndrome.
- Familial factor.
- Familial colorectal cancer syndrome (Lynch I). Hereditary nonpolyposis colorectal cancer (HNPCC) is inherited as an autosomally dominant pattern with 90% penetrance.
- Hereditary adenocarcinomas syndrome (Lynch II). Chromosome defects are inherited at birth and are present in every cell in the body.
- Long-standing ulcerative colitis or Crohn's diseases of the colon, approximately 30% after 25 years if the entire colon is involved.
- Smoking. Men and women smoking during the previous 20 years have three times the relative risk for small adenomas (<1 cm) but not for larger ones. Smoking more than 20 years was associated with a 2.5 relative risk for larger adenomas.
- Dietary factors. It is believed that carcinogens are present in feces. Mutagens are present in animal fats and meat and food poor in fiber. Increased fat and cholesterol ingestion can be also associated with increased risk for CC. Persons with an increased intake of dietary vitamin D and calcium, vitamin A and C, cellulose and wheat bran have a decreased risk for colon cancer. Persons who consume more fat have more bile acid secretion and so increased risk of colon cancer.
- Chronical constipation.
- Physical inactivity. People, who are physically active, are at a lower risk of developing colorectal cancer.
- Virus.
- Alcohol.

There are five metastases of colorectal cancer

- Virchow's metastasis of supraclavicular, on the left side.
- Sister Mary Joseph metastasis in the umbilicus.
- Crukenberg metastasis in ovary in women.

- Schnitzler's metastasis on peritoneum pouch of Douglas.
- Growth into stomach wall.

Cellular classification

Histologic types of colon cancer are as follows:

- Adenocarcinoma (most common colon cancer) – 95%
- Mucinous (colloid) adenocarcinoma.
- Signet ring adenocarcinoma.
- Scirrhus tumors.
- Neuroendocrine. Tumors with neuroendocrine differentiation typically have a poorer prognosis than pure adenocarcinoma variants.

Clinical presentation

Usually patients may be asymptomatic. When symptoms occur, they depend on the site of the lesion. The nearer the lesion to the anus, the more bowel symptoms occur:

- pain in the abdomen (severe pain);
- constipations;
- constipations are replaced by periodical diarrhea;
- iron deficiency anemia;
- anorexia;
- fever;
- asthenia, weakness;
- tumor can be palpated;
- weight loss;
- bloody stools;
- stools with mucus;
- feeling of incomplete defecation (rectal cancer);
- reduction in calibre of feces (rectal cancer).

Metastatic symptoms

There may also be symptoms attributed to distant metastasis:

- shortness of breath (lung metastasis);
- epigastric or right upper quadrant pain, (liver metastasis).

Diagnosis

There are tests for the rectum, rectal tissue, and blood examination and colon cancer detection diagnosing.

- History.
- Physical examination: an exam of the body to check anything that seems unusual.
- Fecal occult blood test: checks stool for blood that can only be seen with a microscope.
- Endoscopy or barium enema assesses the entire colonic mucosa. Flexible endoscopy is not always reliable, rigid sigmoidoscopy is necessary to assess the exact location of the tumor.
- CT scan (CAT scan): a procedure that makes a series of detailed pictures of areas inside the body, taken from different angles. The pictures are made by a computer linked to an X-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly.
- MRI (magnetic resonance imaging): a procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas inside the body. This procedure is also called nuclear magnetic resonance imaging (NMRI).
- Sigmoidoscopy or colonoscopy and biopsy: can show polyps, abnormal areas, or cancer. A sigmoidoscopy or colonoscopy is inserted through the rectum into the colon. Polyps or tissue samples may be taken for biopsy.
- X-ray investigation with barium enema, contrast dye.
- Contrast barium enema – enema containing barium sulfate is administered, thin layer of barium over the inner lining of the colon is visible on X-ray films.
- Blood cell counts: can indicate metastasis of adenocarcinoma.
- Genetic testing for families, who may have a hereditary form of colon cancer.
- Positron emission tomography (PET) is a 3-dimensional scanning technology where a radioactive sugar is injected into the patient, the sugar is collected in tissues with high metabolic activity, and an image is formed by measuring the emission of radiation from the sugar.

Classification of colorectal cancer by TNM system

As colon cancer progresses from Stage 0 to Stage IV, the cancer cells grow through the layers of the colon wall and spread to lymph nodes and other organs.

| | |
|-------------|----------------|
| Stage 0 | Tis, N0, M0 |
| Stage I | T1-2, N0, M0 |
| Stage II A | T3, N0, M0 |
| Stage II B | T4, N0, M0 |
| Stage III A | T1-2, N1, M0 |
| Stage III B | T3-4, N1, M0 |
| Stage III C | T1-4, N2, M0 |
| Stage IV | T1-4, N0-2, M1 |

Grouping of colorectal cancer in stages

- Stage 0 (Carcinoma in Situ)
- In stage 0, cancer is found only in the innermost lining of the colon. Stage 0 cancer is also called carcinoma in situ.
- **Stage I**
- In stage I, cancer has spread beyond the innermost tissue layer of the colon wall to the middle layers. Stage I colon cancer is sometimes called Dukes' A colon cancer.
- **Stage II**
- Stage II colon cancer is divided into stage IIA and stage IIB.
- Stage IIA: cancer has spread beyond the middle tissue layers of the colon wall or has spread to nearby tissues around the colon or wall or has spread to nearby tissues around the colon or rectum.
- Stage IIB: cancer has spread beyond the colon wall into nearby organs and/or through the peritoneum.
- Stage II colon cancer is sometimes called Dukes' B colon cancer.
- **Stage III**
- Stage III colon cancer is divided into stage IIIA, stage IIIB, and stage IIIC.
- Stage IIIA: cancer has spread from the innermost tissue layer of the colon wall to the middle layers and spread to as many as 3 lymph nodes.

- Stage IIIB: cancer has spread to as many as 3 nearby lymph nodes and has spread:
 - Beyond the middle tissue layers of the colon wall;
 - To nearby tissue around the colon or rectum;
 - Beyond the colon wall into nearby organs and / or through the peritoneum.
- Stage IIIC: cancer has spread to 4 or more nearby lymph nodes and has spread:
 - To or beyond the middle tissue layers of the colon wall;
 - To nearby tissue around the colon or rectum;
 - To nearby organs and/or through the peritoneum.
- Stage III colon cancer is sometimes called Dukes' C colon cancer.
- **Stage IV**
- In stage IV, cancer may have spread to nearby lymph nodes and has spread to other parts of the body, such as the liver or lungs. Stage IV colon cancer is sometimes called Dukes' C colon cancer.

Differential diagnosis of colorectal cancer or hemorrhoid or dysentery is made in case if elderly patient has blood and mucus stool. Cecum and ascending colon cancer must be differentiated from appendicular inflammation, anemia of other reasons, tumor of the right kidney, retroperitoneal tumors, tubo-ovarian cyst or ovarian carcinoma in women.

Treatment

Primary tumors should be removed surgically. Pre- or postoperative radiation therapy is beneficial in preventing local recurrences in rectal carcinoma. Operation can be radical, palliative and symptomatic.

Surgical treatment

The treatment includes hemicolectomy (Fig. 11, 12, 13, 14, 15, 16) and sigmoid colectomy.

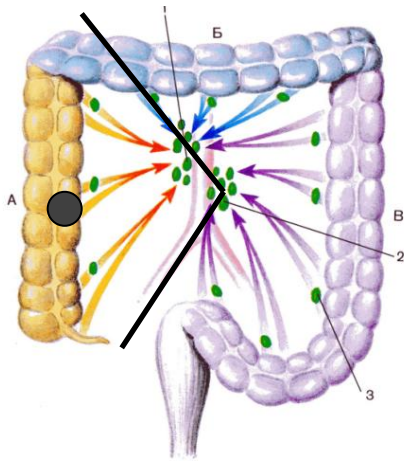


Fig. 11. Right hemicolectomy

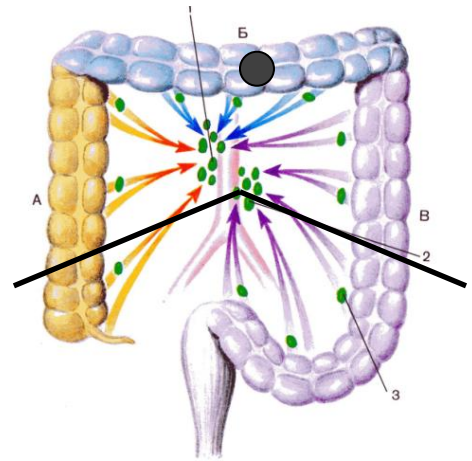


Fig. 12. Transverse colectomy

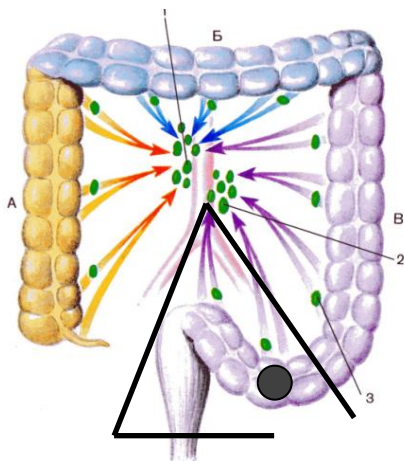


Fig. 13. Sigmoid colectomy

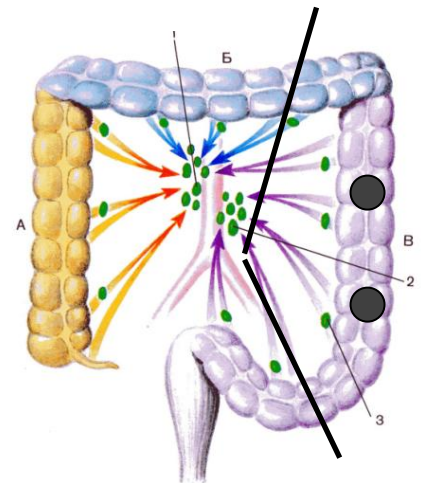


Fig. 14. Left hemicolectomy

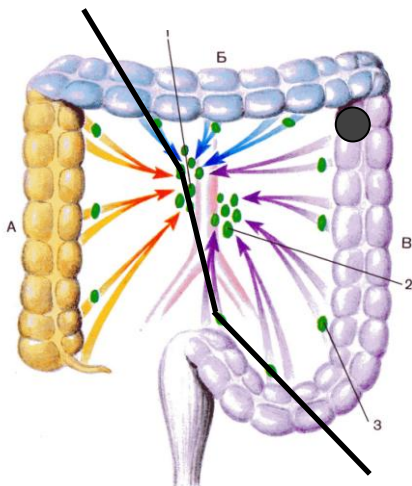


Fig. 15. Left hemicolectomy

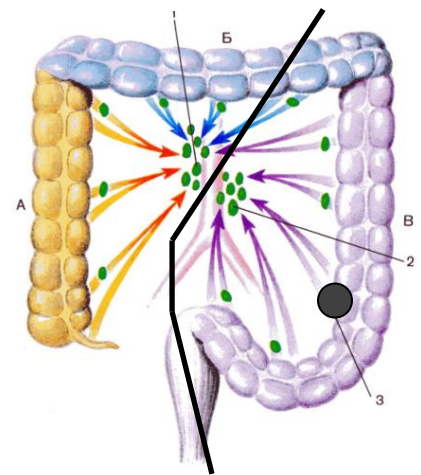


Fig. 16. Left hemicolectomy

Surgery is the primary treatment of colorectal cancer with resection of the segment of the involved intestine and reanastomosis. Colon cancers are removed by a wide resection of the primary lesion together with all mesentery that contains lymph nodes to which the tumor is likely to spread. If the tumor involves adjacent organs such as the small bowel, bladder, uterus, or ovaries, then en bloc resection is indicated. Areas of residual disease should be marked with hemoclips for subsequent radiation therapy.

For radical surgery treatment of cancer of ascending or descending part of the colon the operation of right – side or left – side hemicolectomy with intra-abdominal anastomosis is performed. In sigmoid and high rectal lesions bowel resection with intraabdominal anastomosis may not be possible. In these cases it is necessary to perform Hartman's operation.

Hartman's operation is the radical surgery with the formation of artificial anus in proximal segment of colon after cancer removal. Hartman's operation is made in the following cases: when intestinal obstruction is revealed during surgery, or when tumor is localized at distance 2 up to 8 cm from anus.

Colostomy (Fig. 17) is a formation of artificial anus in abdomen.

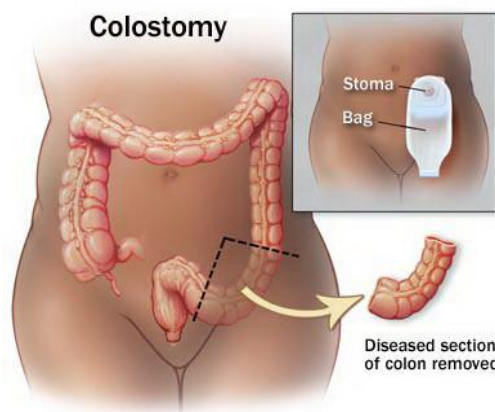


Fig. 17. Colostomy

Radiation therapy

Patients whose tumours lie within 15 cm of the anal verge and go through the bowel wall or involve regional lymph nodes are benefited by postoperative adjuvant radiation therapy, which may be enhanced by the use of radiation sensitizers. Preoperative therapy may also be valuable.

Radiation treatment requires 40 Gy to 50 Gy for large fields that include the entire pelvis and the bifurcation of the aorta.

Chemotherapy

Chemotherapy is carried out after radical surgery in case of metastatic spread into regional lymph nodes (stage II-III).

Chemotherapy with 5 – fluorouracil (5-FU) and metronidazole has proven to be of value when used as a radiation sensitizer. Anal cancer seems to respond well to radiation and 5-fluorouracil plus mitomycin chemotherapy.

Prognosis:

Distant results of radical resection depend on the colorectal cancer stage.

5 – years survival – 80% (stage I and II).

10 - years survival – 74% (stage IIIB).

5 - years survival – 46% (stage IIIB).

10 - years survival – 36% (stage IIIB).

5 - years survival – 5.4% (stage IV).

10 - years survival – 5% (stage IV).

Questions for self control

1. Name the countries with the highest and lowest incidence of colorectal cancer.
2. What are the risk factors?
3. What metastases of colorectal cancer are known?
4. What are the methods of colorectal cancer diagnoses?
5. What are the main pre – cancerous disease of the colon and rectum?
6. How is colorectal cancer treated?

Tests (choose the correct option)

1. Most colorectal cancers develop at the age of

- a) 54;
- b) 64;
- c) 74;
- d) 84.

2. The first sign of CC is

- a) constipation;
- b) pain in the abdomen;
- c) fever;
- d) bloody stools;

3. Differential diagnosis of CC or hemorrhoid or dysentery is made in case if elderly patient has

- a) vomiting;
- b) weight loss;
- c) blood and mucous stool;
- d) anorexia.

4. is the basic method in diagnosis of CC.

- a) X – ray investigation with barium enema and colonoscopy;
- b) ultra – sound;
- c) blood test;
- d) physical examination.

5. Risk factors for development of CC are

- a) age;
- b) smoking;
- c) precancerous disease;
- d) all above mentioned.

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

LUNG CANCER

Lung cancer (LC) (Fig. 18) is the leading malignancy in both men and women. Most lung carcinomas are diagnosed at advanced stage. It is desirable to diagnose lung cancer at an early and potentially curable stage. Most patients, who develop lung cancer, smoke and have smoking – related damage to the heart and lungs. The base of central lung cancer pathogenesis is metaplasia of bronchial epithelium. Lung cancer is the malignant tumor developing from an epithelium of bronchi mucous or in cicatrix of lung parenchyma. The lung cancer is the group of tumors differing by biological nature, clinical signs, morphological structure, speed of growth and ability to metastasize.

Incidence.

Lung cancer is the second most common malignancy after prostate cancer in men and breast cancer in women in the various countries of the world. Lung cancer incidence is increased in urban areas, especially in industrial centers, chemical, and petroleum industries. In Ukraine the incidence of lung cancer was 36.4 per 100000 population in 2012 year (63.9 cases in men, 12.8 cases in women).

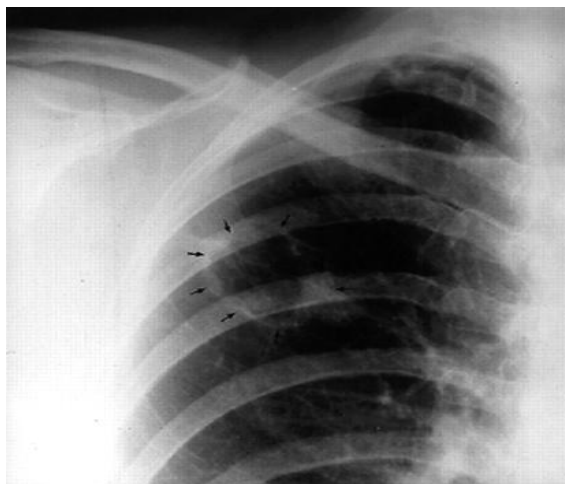


Fig.18. Lung cancer

Risk factors

The are chemical, physical and genetic theories of carcinogenesis. Environmental factor is considered to be the main.

- Smoking – is the cause of lung cancer in 90% of patients. The risk of developing lung cancer is 13 times that of a person, who has never

smoked. A 35 – year – old man who smokes 25 cigarettes or more per day has a 13% risk of dying from lung cancer before the age of 75, a 10% chance of dying from coronary heart disease, and a 28% chance of dying from smoking – related disease.

The risk for lung cancer increases with the number of cigarettes smoked, the duration of smoking, earlier age at the beginning of smoking, degree of inhalation and nicotine content. If a person stops smoking, the risk of lung cancer increases for the first 2 years and then gradually decreases, but it never returns to the same level as that of a person, who has never smoked.

- Passive smoking – is a potential carcinogen. Cigarette smoke contains N - nitrosamines and aromatic polycyclic hydrocarbons, which act as carcinogens.
- Patients cured from lung tuberculosis.
- Patients with inflammatory chronic lung diseases (chronic bronchitis, chronic pneumonia).
- Exposure to carcinogens such as asbestos, radon, polycyclic aromatic hydrocarbons, chromium, nickel and inorganic arsenic compounds:
 - Silicate type of asbestos fiber is an important carcinogen. Asbestos exposure increases the risk of developing lung cancer by 5 times. It has been proved that asbestos exposure leads to lung cancer malignant plural mesothelioma, and pulmonary fibrosis.
 - Radon is the gas, produced as a result of uranium decay. Radon exposure causes 2100 new lung cancer cases each year.
- Ionizing radiation may increase the risk of small cell lung cancer in both smokers and nonsmokers.
- Genetic theory. People genetically predisposed to malignant tumors and having malignances in close relatives.

Pathophysiology

Metaplasia of bronchial epithelium (which is caused by smoking) and chronic inflammatory processes are the base of pathogenesis of central lung cancer.

The cictrix on the lung parenchyma caused by tuberculosis or fibrosis are the base of peripheral lung cancer. Basal cells of bronchial epithelium are the original of lung cancer. Non – small cell lung cancer (NSCLC) is divided into adenocarcinoma, squamous cell carcinoma, large cell carcinoma.

The treatment is the same but histology and clinical characteristics are different. It is possible that LC can exhibit 2 or more histologic patterns.

Adenocarcinoma (35 – 40% of LC) usually occurs in a lung peripheral location and arises from bronchial mucosal glands. Adenocarcinomas form glands and produce mucin. Adenocarcinomas are divided into: 1) acinar, 2) papillary, 3) bronchoalveolar and 4) mucus – secreting.

Bronchoalveolar carcinoma is a clinopathologic entity that arises from type II pneumocytes, grows along alveolar septa and may reveal itself as a solitary peripheral nodule or a pneumonic form, which can spread from one lobe to another. It may occur in those who don't smoke. Squamous cell carcinoma (25-30% of LC) occurs predominantly in a central location.

Non – Small – Cell Lung Cancer (10-15% of LC) has sheets of highly atypical cells with focal necrosis and it is composed of large cells with prominent nucleoli, without mucin production or intercellular bridging.

Histologic classification

- **Adenocarcinoma** is the most frequently occurring type NSCLC, representing 15% - 20% of all lung cancers. The World Health Organization classification of lung cancer divides adenocarcinomas into (1) acinar, (2) papillary, (3) bronchoalveolar and (4) mucus – secreting.
- **Squamous cell carcinoma** accounts for 40% of all lung cancers. It has a distinct dose – response relation for smoking and usually develops in the proximal bronchi, progressing through stages of squamous metaplasia to carcinoma in situ. Well – differentiated squamous cell carcinomas demonstrate keratin pearls, while poorly differentiated squamous cell carcinomas have positive keratin staining.
- **Non – Small – Cell Lung Cancer (NSCLC). Large cell carcinoma** is the least common of all NSCLCs, and accounts for 10 - 15% of lung cancers. It has prominent nucleoli, and no mucin production or intercellular bridging is identified.
- **Small – cell carcinomas** account for 20 – 25% of lung cancer cases and usually develop proximally as large, bulk, soft, grey – white

masses. SCLC is characterized by small cell with, darkly staining nuclei and scanty cytoplasm. It is difficult to diagnose SCLC but fine – needle aspirations of lymph nodes, applying immunohistochemical markers can be helpful. Biochemical and immunologic reagents allow pathologists to distinguish SCLC from NSCLC.

- **Other carcinomas – 10%.**

Metastatic diseases

- 1) Lymphogenic – bifurcation lymph nodes (Fig 19).

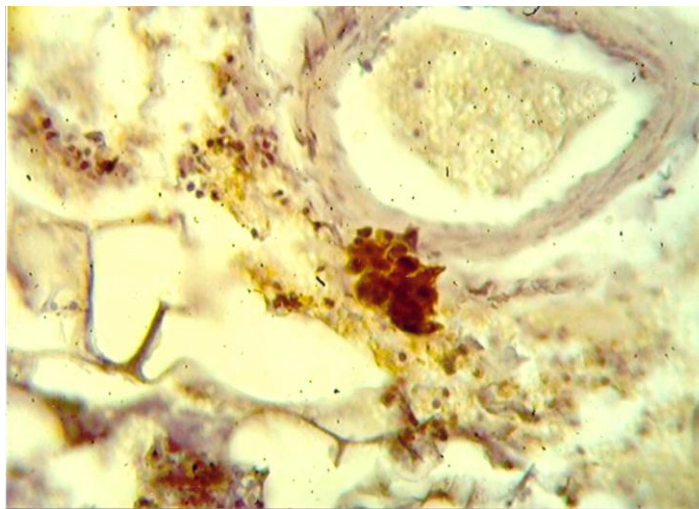


Fig. 19. Tumor cells cluster in lymph node (immunohistochemistry).

- 2) Hemotogenic – lung, liver, kidney, bones, epinephroses, bone marrow, spinal cord (Fig 20).

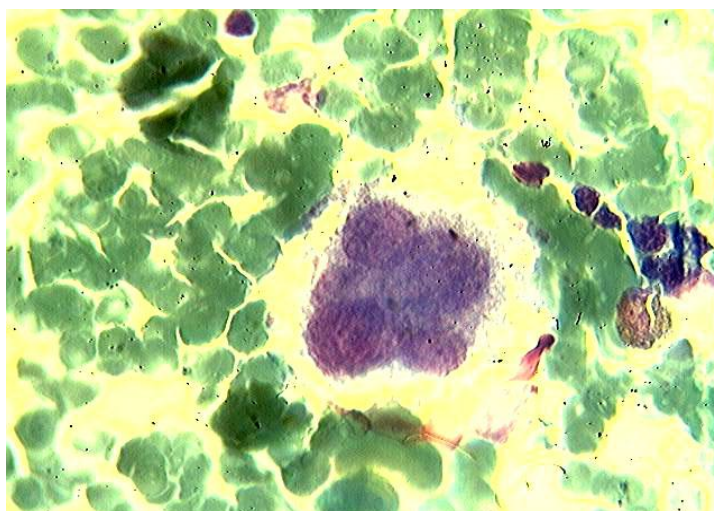


Fig. 20. Bone marrow at light microscopy.

Classification of LC by TNM system is used for all lung carcinomas except SCLC

In the TNM system, there are 4 stages of non – small cell lung cancer subdivided into I-II and A or B subtypes. These stages have important therapeutic and prognosis implications. The stages are as follows:

Primary tumor

- Tis – carcinoma in situ
- TX – positive malignant cytologic findings, no lesion observed.
- T1 – diameter of 3 cm or smaller and surrounded by the lung or visceral pleura or endobronchial tumor distal to the lobar bronchus.
- T2 – diameter greater than 3 cm; extension to the visceral pleura, atelectasis, or obstructive pneumopathy involving less than one lung; lobar endobronchial tumor; or tumor of a main bronchus more than 2 cm from the carina.
- T3 – tumor at the apex; total atelectasis of one lung; endobronchial tumor of a main bronchus within 2 cm of the carina but not adjacent structures such as the chest wall mediastinal pleura, diaphragm, pericardium parietal layer, or mediastinal fat of the phrenic nerve.
- T4 – invasion of the mediastinal organs, including the esophagus, trachea, carina, great vessels, and / or heart; obstruction of the superior vena cava; involvement of a vertebral body; recurrent nerve involvement malignant pleura or pericardial effusion; or satellite pulmonary nodules within the same lobe as the primary tumor.

Regional lymph node involvement

N0 – no lymph nodes involved.

N1 – the ipsilateral bronchopulmonary or hilar nodes involved.

N2 – the ipsilateral mediastinal nodes or ligament involved.

The upper paratracheal / lower paratracheal nodes.

The pretracheal and retrotracheal nodes.

The aortic and aortic window nodes.

The para-aortic nodes.

The para – esophageal nodes.

The pulmonary ligament.

The subcarinal nodes

N3 – the contralateral mediastinal or hilar nodes involved or any scalene or supraclavicular nodes involved.

Metastatic involvement

M0 – no metastases

M1 – metastases present.

Grouping of lung cancer in stages

Stage Ia – T1N0M0

Stage IB – T2N0M0

Stage IIA – T1N1M0

Stage IIB – T2N1M0 or T3N1M0

Stage IIIA – T1-3N2M0 or T3N1M0

Stage IIIB – any T4 or any N3M0

Stage IV – any M1

Lung Cancer Classification according to A. I. Savitsky.

Centrally located lung cancer (80%) affects bronchi (main, lobar, segmental) localizes closely to heart, esophagus, large vessels (Fig 21).

Centrally located lung cancer patterns of growth

Peribronchial nodal

Endobronchial

Remified (ramous branched)



Fig. 21. Different patterns of central Lung cancer growth.

Peripheral forms (15-30%) of lung cancer develop in bronchi of finer size and far from the vital organs.

1. Round tumor
2. Pneumonia like cancer
3. Cavitory cancer
4. Pancoast's cancer – results from the tumor growth in the apex with involvement of the eighth cervical and first and second thoracic nerves.

Tumor grows into the first rib, causes rib destruction, pain in the top extremity on the side of the lesion and development of Horner's syndrome (ptosis, miosis, enophthalmos).

Atypical forms 5% LC

1. mediastinal;
2. miliar carcinosis;
3. bone;
4. brain;
5. cardiovascular;
6. liver;
7. gastrointestinal.

Lung cancer clinical manifestation

There are two groups of lung cancer symptoms

The clinical picture of LC depends on the type of the tumor growth, clinical-anatomic form of LC, rates of growth and initiation, accompanying secondary inflammatory changes.

There are three groups of LC symptoms: local, secondary and general symptoms.

Local symptoms

- cough (whooping cough);
- coughing up blood (hemoptysis);
- dyspnea;
- chest pain on the side of the lesion sometimes on the contralesional;
- compression syndrome (superior vena cava (svc) obstruction).
- Pancoast's syndrome.

Secondary symptoms

- subfebrile temperature;
- dysphagia;
- pleurisy;
- hemorrhagic effusion;

- recurrent laryngeal nerve paresis;
- hoarseness.

General symptoms

- paraneoplastic syndrome (pain in joints);
- weight loss;
- anorexia;
- fatigue;
- weakness;
- cachexia (poor prognostic factor);
- anemia (normocytic, normochromic);
- thrombophlebitis migrans;
- chronic hemorrhagic diathesis;
- hyperthrophic pulmonary osteoarthropathy.

Diagnosis

- History (smoking, tuberculosis).
- Sputum cytology. Up to 80% of central tumors can be diagnosed with three sputum samples. The yield is smaller for peripheral tumors (20%). Cytology diagnoses squamous cell tumors more frequently than adenocarcinoma or large cell tumors.
- Physical examination of the chest detects partial or complete obstruction of airways, atelectasis or pneumonia, and pleural effusion. Particular attention should be paid to the head and neck (for concomitant cancers); to lymph node areas in the supraclavicular fossa, neck, and axilla (for metastases); and to the abdomen (for organomegaly).
- Palpation of lymph nodes
- Chest x-ray (demonstrates the size of the tumor, especially in peripheral lesions except for rare occult tumor. Central tumors may be associated with atelectasis or obstructive pneumonitis).
- Flexible fiberoptic bronchoscopy with biopsy can have diagnostic yield more than 90%. Flexible fiberoptic bronchoscopy is one of the main methods in diagnosis of LC. It allows to examine trachea; main, lobular, segmentary and subsegmental bronchi; to see directly a tumor and to estimate its size and, that it is especially important, localization. Tumor localization frequently allows to define volume of surgery

(pneumonectomy, lobectomy, bilobectomy) or impossibility of its performance.

Except for intrabronchial diffusion the bronchoscopy indirectly allows to define extrapulmonary diffusion of tumor metastases (subcarinal and paratracheal lymph nodes).

The greatest accuracy of the diagnosis is given not by visual diagnose of a tumor, but histological examination of the material received by biopsy.

- Transbronchoscopic needle aspiration through the airway wall can confirm the presence of malignancy in mediastinal lymph nodes.
- Transthoracic punch biopsy.
- Transesophageal fine – needle biopsy of lymph nodes under endoscopic guidance.
- Cervical mediastinoscopy is the most accurate lymph node staging technique to assess superior mediastinal lymph nodes, which can be involved in this disease.

Toracotomy

Complete blood cell (CBC) count allows to find out in the majority of patients with LC (75 %) increasing ESR (more than 30 mm/hour). Change of this parameter is observed in patients with central and peripheral LC.

- CT scan can confirm abnormalities seen on plain chest X – ray film of the mediastinum for the staging of lung cancer has been reported to have an overall accuracy of 70%. Mediastinal lymph nodes are considered abnormal when they are larger than 1.5cm in diameter and normal when smaller than 1.0 cm; nodes between these two limits are indeterminate. CT scan of the thorax is superior to chest x-ray and MRI. CT scanning (Fig. 22.) provides information about extent and invasion of the primary tumor and presence of pleural effusion as well as information about lymph node status. If a 1.5cm limit is used to call a node abnormal, sensitivity is relatively poor, but specificity is excellent. Conventional tomography is reported to be superior to CT in assessing hilar adenopathy.



Fig. 22. Thorax CT peripheries bronchialcarcinom.

- MRI scans are not part of the routine staging workup of SCLC, even though they have been shown to detect abnormal bone marrow signal in patients with bone marrow metastasis. MRI scans have an increased ability to detect disease in proximity to neurovascular structures. MRI examination is considered standard in the workup of patients in whom spinal cord compression is suspected.
- Positron emission tomography (PET) scanning is still under evaluation for lung cancers and, to date, has had its greatest application in NSCLC, in which it is used to more accurately stage patients prior to anticipated surgery.
- Bone scintigraphy. The skeletal system is another common site of metastases for lung cancers. If patients report bone pain or if their serum calcium and/or alkaline phosphatase levels are elevated, bone scan should be obtained to search for bone metastases.
- Bone marrow aspiration and biopsy if there are abnormalities in CBC or peripheral smear. Bone marrow examination is necessary in patients in whom myelophthisic anemia is suspected.

Complicated lung cancer

- **The compression of vena cava superior** (cava-syndrome) develops in the result of this vessel compression directly by a right lung tumor or by cancer metastases in a mediastinum. Vena cava superior is a unique vessel along which the blood comes back to heart from head, neck, top extremities and the upper half of trunk. Decompensation comes after vein compression or invasion by a tumor, when the blood from the specified departments of the body may not return to the right auricle, and venous stagnation develops. It manifests in various objective and subjective attributes: cyanosis of seen mucosas and face

skin; face or top extremities edema, expansion of hypodermic veins of neck and anterior thoracic wall; the venous network reminds the head of a jellyfish (Caput medusae); hum and gravity in a head.

- **The esophago-bronchial fistula** is the most severe LC complication. The pathological junction of bronchi and esophagus is the result of disintegration or radial destruction of LC. Esophago-bronchial fistula formation manifests itself clinically in fits of coughing in the process of solid and soft food and liquids intake. Esophagus X-ray with contrast agent use shows that its passage is taped from an esophagus to a bronchial tree. Aspirational pneumonias development worsens fast the patients condition. The doctors should do their best to stop the food and liquid penetration into bronchi from esophagus and prevent pneumonia.
- **The profuse pulmonary bleeding** in patients with LC is the result of tumor disintegration and bronchial branches or pulmonary vessels erosion. The pulmonary bleeding is characterized by the fits of coughing with the following scarlet foamy blood secretion from a mouth. Sometimes patients choke, without having time to expectorate blood. Paleness of skin, cold sweat, syncope, tachycardia, arterial hypotension are marked. Plural atelectasises and the centers of aspirational pneumonias develop in lungs.
- **The lung atelectasis** develops as the result of tumor obturation of a main bronchus and leads to short wind, chest pain, tachycardia. Radiologically the massive opacity (lung without air) and shift of a mediastinum to the side of the atelectasis are taped.

Treatment

The main method of lung cancer treatment is surgery. Since most lung cancers cannot be cured the appropriate application of skilled palliative care is an important part of the treatment of patients with NSCLC.

Surgical treatment of the Non – Small Cell Lung cancer

- Contraindications for surgical treatment are: the distant metastases, metastases into pleura, tumor invasion into heart, aorta, trachea and presence of specific pleuritis, the respiratory failure, heart pathology. The top age limit is not determined. Nowadays the patients over 70 years undergo surgical treatment.

- The standard surgical treatment is: lobectomy, bilobectomy, pneumonectomy, expanded pneumonectomy (fat removing of a mediastinum), combined pneumonectomy (removing of the lung with a pericardium site, diaphragm site or thoracic wall site).
- Nowadays bronchoplastic operations make it possible to keep a respiratory lung volume. The most frequent operation is upper lobe removal with the main bronchus circular resection.

Radiation therapy of LC

- Radiation therapy can be used alone and in combination with surgery or chemotherapy.
- Application of gamma-therapy with a radioactive source 50 - 80Gr. (radiation energy 1.25 MeV) is the most widespread, it depends on the histologic tumor structure.
- Spatial distribution of high-energy radiation (5-45 MeV) is especially recommended at deeply posed neoplasms, including LC.
- Destruction of the whole tumor in irradiated volume is the result of radical radiation treatment and provides long – term and proof effect while palliative irradiation ensures only partial tumor destruction. The volume of the exposed, to radical radiation tissues should cover a seen initial tumor, probable lymphogenous metastases: bronchopulmonary, hilar, upper and lower tracheobronchial, paratracheal lymph nodes. Radical radiation program of undifferentiated LC small cell forms provides preventive irradiation of supraclavicular areas and is aimed at subclinical metastases destruction.
- Radiation therapy of peripheral LC has its own peculiarities. Tumor shadow, radiological "path" to a lung hilar (which is infiltration of a peribronchial and perivascular tissue by tumor), zones of regional lymph nodes are the field of irradiation.
- Radiation treatment is the method of choice for the mediastinal form of LC and any other form with massive innidation in lymph nodes of mediastinum complicated with large veins compression causing development of the mediastinal compression syndrome.
- Contraindications for radical radiation therapy for LC are distant metastases and pleural or pericardial effusions. Endobronchial brachytherapy is a type of radiation techique which is used clinically. In brachytherapy, the radiation device is placed within or close to the target volum.

The most commonly used isotopes have been radon α 198 Au. Recently iridium has been used.

Brachytherapy allows the precise localization of dose in the tumor and to spare adjacent normal tissues because of the limited penetration of the low – energy emission.

Palliative brachytherapy with ^{192}Ir improves the quality of patients life, however some complications such as bleeding or broncho – esophagus fistula formation (10 – 15%) have been observed.

Chemotherapy of LC

The hematological control is obligatory within 7 - 12 days after the end of the course of chemotherapy. Oppression of hemopoiesis function: downstroke of leucocytes and thrombocytes amount and anemia are the most common complications.

60% of the patients with NSCLC have stage IIIB or IV disease they are indicated chemotherapy alone as palliative treatment (because of malignant pleura effusion).

Patients with locally advanced NSCLC are given chemotherapy as a part of multimodality therapy. Chemotherapy is the most common method of SCLC treatment (etoposide, carboplatin or cisplatin regimens are believed to be the best combination of efficacy and lack of toxicity).

Platinum-based chemotherapy provides better palliative benefits than the best supportive care. Commonly used regimens include carboplatin – paclitaxel, cisplatin – gemcitabine, and cisplatin - vinorelbine, all of which achieve similar results.

Tumor histological type is of special value for LC chemotherapy. It defines character of chemotherapy and the forecast for effect of treatment and prognosis.

Prognosis

The postoperative lethality in patients who underwent radical resection of lung tumors varies from 3 to 9 %. Prognosis depends on disease stage and biological properties of a tumor. The most adverse forecast have undifferentiated cancers (small cell and macrocellular). The five - year survival rate after surgical LC treatment is 30%. 80 % of patients who have been treated in stage T1-2N0M0 have the 5 - year survival rate.

5 – year survival rates:

Stage IA – 75%.

Stage IB – 55%.

Stage IIA – 50%.

Stage IIB – 40%.

Stage IIIA – 10-35%.

Stage IIIB – 5%.

Stage IV – 5%.

Questions for self control

1. What are the symptoms of LC?
2. What is the incidence of LC in industrial countries?
3. What precancerous diseases increase the risk of LC?
4. What age is LC usually diagnosed at?
5. Etiology and risk factors of LC.
6. Give histologic classification of LC.
7. What is LC classification according to Savitsky?

Tests (choose the correct option)

- 1. Lung cancers occur in 90% in**
 - a) uranium miners;
 - b) heavy drinkers;
 - c) engineers.
- 2. Centrally located forms of Lung cancer account for 80% of all lung cancers**
 - a) False.
 - b) True.
 - c) None of the above.
- 3. is the most common cause of superior vena cava obstruction**
 - a) Tuberculosis.
 - b) AIDS.
 - c) Lung cancer.

4. 60% of the patients with NSCLC have stage IIIB or IV, they are indicated:

- a) radiation therapy;
- b) surgery alone;
- c) chemotherapy alone as palliative treatment;
- d) cryotherapy.

5. Common site of small cell lung cancer spread includes all except

- a) brain.
- b) bones.
- c) adrenals.
- d) prostate gland.

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

BREAST CANCER

Incidence.

Breast cancer (BC) is the most common malignancy among women (excluding cancers of the skin) and accounts for 27% of women cancers. BC constitutes 18% of all female cancers. The incidence of BC is increasing in many countries annually (1 million of new BC cases). In Ukraine the incidence of breast cancer was 36.4 per 100000 population in 2012 year (in men 0.6, in women 67.1 cases).

The highest incidence is in the age group of 45 – 75; it is rarely observed under 35 years. BC ranks first among cancer deaths in women in the world. Men can also develop BC but male BC is very rare, less than 1% of all BC cases.

Risk factors

The breast are hormonally responsive organs. So breast cancer is hormone – relative tumor. The increased level of estradiol and decreased level of globulin, which connects the steroid sex hormones is found in the blood of breast cancer patients. Hyperestrogenemia and reduction of ability to connect estrogens may be the results of lifestyle features, reproductive history, race and diet (risk factors).

- Female sex.
- History (anamnesis).
- Preinvasive cancer:
 - lobular carcinoma in situ;
 - ductal carcinoma in situ;
- Early beginning of menstruating and menopause after the age of 55 years.
- Late pregnancy.
- Pregnancy interruption.
- Mammary gland injury (with hematoma).
- Smoking and alcohol consumption.
- Genetic predisposition (2 first degree relatives) – women, who have a first degree relative (mother, sister, daughter), diagnosed with breast cancer are at increased risk of the disease. More than one first – degree relative with breast cancer elevates that risk.
- Diabetes mellitus

- Overweight and obesity > 80
- Social class

There are four pathogenetic forms of BC

Hypothyreoid form is observed in 4.3 % of the patients in the age under 30 suffering with hypothyroidism, early obesity, follicular cyst of ovaries, early occurrence of menses.

Ovarian form is met approximately in half of the patients aged 28-50. These are the women with expressed ovaries dysfunction, sex frustration, inclined to hormonal dysplasias of breast. These are also women with late labors and predisposition to obesity.

Adrenal form is observed in 40 % of the patients in which the disease is connected with dysfunction of paranephroses. Tumors of this form grow infiltratively and are inclined to an early generalization.

Senile form is observed in 8 % of the patients over 60.

BC disseminates by lymphatic and blood vessels, and also by lactiferous ducts. Regional lymphatic collectors are axillary, subscapullary, subclavial, supraclavial and intrathoracic parasternal lymphatic nodes. The hematogenous diffusion of metastases is going by venous channel, which begins from the intercostal veins. With flow of blood cancer cells go into internal organs, bones, etc. Lungs, pleura, liver, brain, ovaries are "target" organs of BC metastases. Bone metastases most frequently are localized in pelvic bones, backbone, ribs, large tubular bones.

Classification of BC by TNM system

T – primary tumor;

Tx – primary tumor cannot be assessed;

T0 – no evidence of primary tumor;

Tis – preinvasive carcinoma (cancer in situ) or Paget's disease of a nipple without an obvious tumor;

T1 – tumor up to 2 cm in the greatest dimension;

T2 – tumor up to 5 cm in the greatest dimension;

T3 – tumor more than 5 cm in the greatest dimension;

T4 – tumor of any size with direct extension to chest wall or skin;

N - regional lymph nodes:

Nx – regional lymph nodes cannot be assessed;

- N0 – no regional lymph node metastases;
 N1 - metastasis to mobile ipsilateral axillary nodes;
 N2 - metastases to ipsilateral axillary nodes fixed to one another ipsilateral or to other structures;
 N3 - metastases to internal mammary lymph nodes lesion.
- M – distant metastasis:**
 Mx - distant metastasis cannot be assessed;
 M0 – no evidence distant metastasis;
 M1 – distant metastasis (including metastases to ipsilateral supraclavicular, lymph nodes);

Grouping of breast cancer in stages

| | | | |
|------------|--------|-----------|-----------|
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage IIA | T1 N1 | M0, T2 | N0 M0 |
| Stage IIB | T2 N1 | N0, T3 | N0 M0 |
| Stage IIIA | T1 - 2 | N2 M0, T3 | N1 – 2 M0 |
| Stage IIIB | T4 | N any | M0, T any |
| Stage IV | T any | N any | M1 |

Histological classification

Breast cancers are almost always adenocarcinomas, seldom are sarcomas, and rarely are epidermoid (squamous) cell carcinomas. Breast cancer histological classifications:

- 1) Carcinomas, NOS (not otherwise specified).
- 2) Ductal.
- 3) Intraductal (in situ).
 - Invasive with predominant intraductal component.
 - Invasive, NOS.
 - Comedo.
 - Inflammatory.
 - Medullary with lymphocytic infiltration.
 - Mucinous (colloid).
 - Papillary.
 - Scirrhous.
 - Tubular.

- Other
- 4) Lobular:
- In situ.
 - Invasive with predominant in situ component.
 - Invasive.
- 5) Nipple:
- Paget's disease, NOS.
 - Paget's disease with intraductal carcinoma.
 - Paget's disease with invasive ductal carcinoma.
- 6) Other:
- Undifferentiated carcinoma

Site is the place where tumor occurs. 70% of BC, are the ducts, 20% begin in lobules and they are called ductal carcinoma and lobular carcinomas. 10% of all breast cancers are medullar, mucinous, tubular or papillary breast cancers.

Spread.

Tumors that have spread outside of the duct and into the surrounding tissue, are called invasive or infiltrating ductal or lobular carcinomas. Those that have not spread are called in situ, meaning "in place" or intraepithelial cancer.

Breast cancer cells may migrate to the blood vessels or the lymph nodes and affect the following nodes:

- Subaxillary
- Supraclavicular
- Subclavian
- Subscapular
- Contraleteral

BC metastasizes to: brain, lungs, liver, kidney, spinal cord, pelvis and pleura, bone, adrenal, spleen, skin, retina, ovary.

Clinical forms of BC

Nodal form 90%:

- Dense (cartilage – like).
- Tuberoid.
- Painless.
- Movable.
- Orange peel appearance (citric crust).
- Umbilication symptom.
- Nipple retraction.
- Nipple discharge.

Diffuse forms 10%:(frequently proceed as acute, extremely malignant tumors. They quickly recur after surgical treatment, roughly metastasize and have the bad prognosis).

Mastitis-similar form is characterized by hyperemia, edema of soft tissues of the part or the whole breast and also by high temperature. It's like acute mastitis and that's why this form is the reason of diagnostic and treatment mistakes (incision of "mastitis", etc.).

Erysipilatous form is one of inflammatory-infiltrative versions of cancer. It's feature is intraskin tumor diffusion by lymphatic vessels of the skin. It is clinically shown that a peristatic hyperemia of the skin is the result of cancer lymphangitis (externally similar to an erysipelas).

Edematous infiltrative form is accompanied by augmentation of breast size, infiltration of the skin ("citric crust"). The palpable infiltrate has not precise borders and occupies the most part of the breast.

Testaceous cancer is characterized by tumoral infiltration of tissue and skin of breast. Process may invade a thoracal wall outside the breast limits. The skin becomes dense, pigmented, unmovable. There are many dense intraskin tumoral nodes. Breast decreases in sizes and tightens up. The tumoral infiltrate pulls together a thoracal wall as a testa.

Rare forms

- *Paget's breast cancer* is the cancer of a nipple area. Nipple tenderness, thickened nipple, pathological discharge from nipple, nipple retraction (Fig. 23), a persistent sore or "racket symptom" (Fig. 24) may occur both in nodular and diffuse forms. In Paget's

cancer there is ulceration of nipple and areolar zone.



Fig. 23. Paget's breast cancer



Fig. 24. Paget's breast cancer

- *Primary-multiple BC* is simultaneous development of two or several tumors in one patient. There are 4 cases of primary-multiple cancer: with simultaneous lesion of two breasts, with localization of two tumors in one breast, with presence of a tumor in one of the breasts and in other organs. The risk of tumor development in the contralesional breast in radically treated patients with BC increases 5-6 times.
- *Occult (latent, nonpalpable)*. It is difficult to palpate tumors smaller than 1 cm. Such tumors are usually not determined by all specific

examinations. Latent form (2-3 mm) is a nonpalpable form. It affects subaxillary lymph nodes.

- *Cancer of additional breast.* Breast tissue gets in axillary area during an embryogenesis. Additional breast presents itself during lactemia.
- *Marginal form of BC* is a nodal form of BC which is in submammary fold.

Every year the number of patients in which BC is diagnosed in preclinical stage is increasing. In the countries of Western Europe more than 30 % of the patients with BC are operated in this stage.

Diagnosis

- A complete history (anamnesis)
 - Breast mass
 - Nipple discharge : spontaneous or induced, color.
 - Nipple and skin retraction.
 - Axillary mass.
 - Arm swelling or pain.
 - History of prior breast biopsies, cyst aspiration.
 - Reproductive history.
 - Age at onset of menses.
 - Date of last menstrual period, regularity of cycles.
 - Number of pregnancies, children, abortions.
 - Age at first birth.
 - Age at menopause.
 - History of hormone use.
 - Family history: relationship, age at diagnosis of breast cancer.
 - Gynecology disease.

Mammary glands palpation

The breast examination should be done in a well – lit room with the patient both lying and standing positions. When the patient is recumbent, her breast should rest easily at the top of the chest wall.

The breast should be thoroughly examined bimanually by rotating the fingers in a circular manner beginning at the areolar margin and gradually working toward the periphery so as to cover the vertical – strip technique and a quadrant – by – quadrant examination. Examination of

the axillary tail is best performed with the patient's arm over her head. The areolar margin should be palpated carefully, as this is a common location for solitary papillomas. Then fingers are to be rolled from the areolar margin towards the nipple to look for nipple discharge. The patient is to be examined both in sitting and standing positions by compressing the breast from above and below between the two palms. The patients should extend her arms overhead and lean toward to detected skin dimpling.

Clinical examination should be done 5 days after the first day of menstrual flow, because breast nodularity and tenderness are least marked at that time. The palpation of breasts is necessary to carry out in a position with the patient standing and laying.

Clinical presentation

The basic clinical displays of BC are:

- Excavation of skin in the place of determined tumor of breast, sign of umbilication or platform;
- The thickening of nipple and areola where the presence of a tumor – Crause's sign is determined;
- Phenomenon of lymphostasis - sign of "citric crust" above the tumor or outside;
- The Koenig's sign: a tumor does not disappear when pressed;
- The Pribram's sign: the nipple tumor is displaced when pandiculated;
- Nipple excavation;
- Pathological nipple discharges (bloody, dark or light liquid).

Physical examination

Breast mass size (measured).

Location (clock position and distance from areola).

Consistency.

Fixation to skin, pectoral muscle, chest wall.

Skin changes.

Erythema.

Edema.

Dimpling.

Satellite nodules.

Ulceration.

Nipple changes

Retraction.

Discoloration.

Erosion.

Discharge: color, location.

Nodes

Axillary size, number, fixation.

Supraclavicular.

Infraclavicular.

Arm edema.

Ultrasound of mammary gland.

Ultrasound visualizes different types of the breast tissue on the basis of differences in acoustic impedance.

Malignancy is determined by:

- a solid mass with irregular margins and heterogeneous internal echoes;
- surrounding flare of bright echoes;
- in case of small or unpalpable lesion, ultrasound may be used to guide fine needle biopsy.

Biopsy. There are following types of biopsy:

- Fine needle aspiration cytology (also called fine needle aspiration) uses a thin needle to withdraw fluid and cells for cytological examination.
- Trepan (Core – needle) biopsy. The core of the tissue is obtained for histologic examination. Ductal carcinoma in situ can be identified.
- Excisional biopsy has been the standard technique for the diagnosis of breast masses. It allows the complete evaluation of the tumor size and its histologic characteristics (the mass excised with a surrounding margin of normal breast tissue).
- Incisional biopsy is used to establish a diagnosis of breast cancer in masses too large to excise completely (patients with metastatic disease or with locally advanced BC who will receive systemic therapy as an initial treatment approach).

Mammography

Mammography is a non – invasive radiographic procedure, which enables the entire breast tissue to be examined. Not palpable breast cancers (nearly 50%) are detected only by mammography. Women over 40 are recommended mammography every two years (Fig. 25).

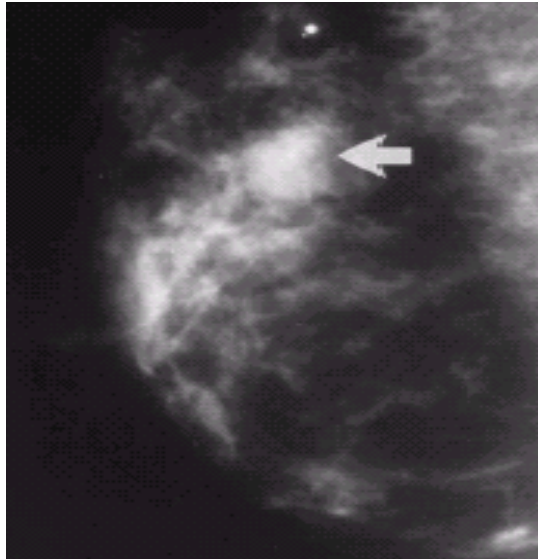


Fig. 25. Mammography

Malignancy may be shown as:

- suspected lesions with ill – defined margins;
- asymmetric areas of density and distortion;
- skin thickening;
- circumscribed lesions with well or poorly defined margins;
- calcifications – variable in size, distribution, form or density.

However:

- approximately 5% of clinically palpable carcinomas are not detectable;
- the method is less accurate in women under 35, who have denser breast;
- successive mammograms incur a cumulative radiation dose, which in itself may be carcinogenic.

Laboratory tests.

1. Estrogen (ER) and progesterone receptor (PR) tests. These help determine both the prognosis (chance of recovery) and whether the cells respond to hormones. Generally, ER or PR positive (+) tumors will respond to hormone therapy. A woman's ER/PR status helps guide treatment decisions.
2. HER – 2/neu tests in mass tissue. This is a gene that is over expressed (too much of it) in about 25% of women with breast cancer. A woman's HER – 2 status helps guide treatment decisions.
3. Blood tests include:
 - Complete blood count (this test measures levels of both red and white blood cells); Differential blood count (this test measures the different types of white blood cells); Platelet count (platelets are the components of blood that help it to clot).
 - Alkaline phosphates levels (high levels of this enzyme could signify disease in the liver, bone cells, and bile ducts).
 - Tumor markers: Carcinoembryonic antigen (CEA), CA 15-3, or CA 27-29 may indicate the presence or degree of cancer.
 - Total bilirubin count and serum glutamate pyruvate transaminase (SGPT) levels (these tests evaluate liver function: high levels of SGPT can indicate liver damage, a signal of possible spread to that organ).

Ductography.

The *ductography* (Fig.26.) is a contrast mammography, which should be carried out after injection of a contrast agent in lactiferous ducts. Indications for this inspection are intraductal papilloma, intraductal cancer.

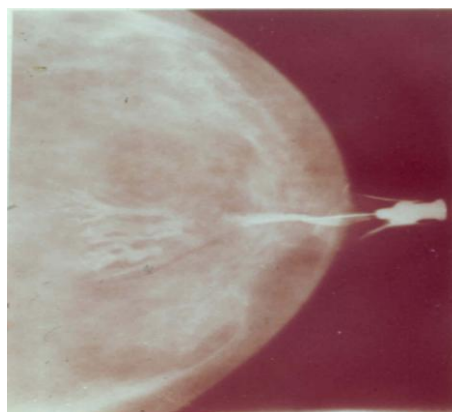


Fig. 26. Ductography

Additional tests:

1. Chest x-ray may be used to look for metastases to the lung.
2. Bone scan may be used to look for metastases to the bones.
3. Computed tomography (CT) scan may be used to look for distant tumors.

CT scan creates a three - dimensional picture of the inside of the body using a series of x-ray pictures that are taken from many different angles. A computer compiles these images into a detailed, cross-sectional view.

4. Positron-emission tomography (PET) scan. The doctor injects a low-dose radioactive sugar (called glucose) solution into the body. A special scanner produces a computerized image of the areas in the body to tell where the sugar is being used. Cancer cells use more sugar than normal cells, this fact helps to improve diagnosis.

Treatment

The most common method of BC treatment is surgery.

BC surgery began with description of the radical mastectomy by Halsted in 1894. Radical mastectomy is the en block removal of the breast, the skin overlying the tumor (usually a 5cm margin), the pectoral major and minor muscles and the auxiliary contents.

Now modified radical mastectomy (Patey's radical mastectomy) is the standard operative treatment with breast cancer. This operation includes removal of the entire breast and all of the axillary lymph nodes. The pectoral minor muscle is removed. The incidence of arm edema and shoulder dysfunction is decreased.

Madden's radical mastectomy includes removal of the entire breast and all of the axillary lymph nodes. The pectoral major and minor muscles are not removed. There is now shoulder dysfunction.

The major options for local treatment are modified radical mastectomy and breast conserving treatment. The latter consists of conservative surgery and irradiation.

Breast salvage surgery involves removal of the primary tumor and a variable marginal of the surrounding normal breast tissue, usually accompanied by an auxiliary dissection.

Surgical therapy of BC: lumpectomy, tumorectomy, segmental mastectomy and local excision (imply the removal of a relatively small amount of normal breast tissue), partial mastectomy and quadrantectomy

(usually imply the excision of a larger amount of breast tissue).

Histologic examination of margins is obligatory.

Clear margin is an area of healthy cells all around the cancer.

In case of cancer cells presence at the edge (margin) of the resected breast tissue a high possibility of BC recurrence occurs and so additional surgery (mastectomy) is recommended.

Local recurrence is reappearance of BC in the surgical or radiation field. The term local recurrence includes tumor in the chest wall, the overlying skin, residual breast tissue, ipsilateral axillary lymph nodes, supraclavicular nodes, or internal mammary lymph nodes.

High local recurrence rates are often seen in women with locally advanced BC treated with surgery alone.

Radiation therapy, chemotherapy, or hormonal therapy are recommended in case of lymph nodes involvement or if a tumor is of a certain size.

Radiation therapy

BC radiation therapy is one of the main components in combined treatment. There are two types of radiation therapy. External radiation therapy uses a machine outside the body to send radiation toward the cancer. Internal radiation therapy uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the tumor.

Radiation can be performed both before or after surgery.

I. Preoperative radiation therapy is carried out in two cases:

Before surgery radiation is aimed at shrinking a large tumor and making it easier to remove.

1. A preoperative irradiation fraction is 2Gr daily a focal dose is 40-50Gr on a field. Patients with stage IIIA and IIIB in N1 and N2 are operated 4-5 weeks after cessation of radiation therapy.
2. Patients with stage IIA and IIB are irradiated by large fraction (4-5) Gr within 5 days, general cooperative dose is 25Gr. The aim is to suppress the most malignant tumor cells. A patient is operated at once after the irradiation before development of radiation reaction.

II. Postoperative radiation therapy follows surgery for destruction of cancer cells which have penetrated into a wound during operation.

Radiation is very effective in reducing the chance of breast cancer

recurrence in both the breast and the chest wall. A postoperative cicatrix, axillary, supraclavicular and parasternal areas are irradiated with a cooperative dose 45Gr on a field.

Hormone therapy

Hormone therapy is used to manage tumors that test positive for either estrogen or progesterone receptors. Hormones are substances produced by glands and circulated in the bloodstream. Some hormones can cause certain cancers to grow. The growth of these types of tumors is limited by blocking the hormones.

Androgens or antiestrogens are used in hormone therapy.

Hormone therapy effect depends on presence or absence of Progesteron (RP) or Estrogen (RE) receptors in tumor. Receptor is a special kind of protein, which binds hormones, necessary for a cell, and transports them in a core. 80% of the patients react to hormone therapy in the case of Progesteron receptors (RP+) and Estrogen receptors (RE+) presence in a tumor. The receptors blocking prevents cancer cells from growing, stop their division, cause their aging and destruction.

Substances capable to selectively block steroid hormones receptors are being synthesized nowadays. They cause the termination of cancer cells division. Substances of such kind are called antihormonal and in this very case antiestrogens. Antiestrogens are to be used for 3 to 5 years and more. Tumor hormone receptors (soluble proteins of cytoplasm in a cell) have ability to make bounds with steroids. The complex hormone – receptor is transmitted to the core, where it interacts with chromatin. The breast tissues contain specific receptors of androgens, glucocorticoids, estrogens and progestinums. The hormone therapy efficiency depends on the presence of steroid hormone reseptors in the tumor tissues. 35 – 85% of the patients have receptor – positive tumors. The hormone therapy with the aromatase inhibitor is given to some postmenopausal women, who have hormone – dependent breast cancer. Hormone – dependent breast cancer needs the hormone estrogen to grow. Aromatase inhibitors decrease the body's estrogen by blocking an enzyme called aromatase from turning androgen into estrogen. Aromatase inhibitors are also being tested in clinical trials to compare them to the hormone therapy for the treatment of metastatic breast cancer.

Chemotherapy

Chemotherapy is cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by cessation of their division. When chemotherapy is taken orally or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the spinal column, an organ or body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). The way the chemotherapy is given depends on the type and stage of the cancer being treated.

Chemotherapy is considered a "systemic" therapy, meaning that it travels throughout the body, unlike surgery or radiation, which are "local" therapies.

- Adjuvant or preventive therapy: therapy is given after surgery to reduce the likelihood of the cancer returning.
- Neoadjuvant therapy: therapy given before surgery to shrink the tumor, allowing the surgery to be more successful.
- Concurrent therapy: 2 or more therapies are given together, such as chemotherapy and radiation.

Chemotherapy can be given in some ways:

- orally;
- intravenously (either as a short infusion or continuously for one or more days)
- as an injection or needle;
- intra – arterially.

The most common adjuvant chemotherapy choices include cyclophosphamide, methotrexate, fluorouracil (CMF), doxorubicin and cyclophosphamide (AC).

In patients with a lesion of regional lymphatic nodes the postoperative chemotherapy (adjuvant or preventive) is carried out (from 3 up to 6 courses of chemotherapy with 1 month interval). As a rule, the polychemotherapy is carried out, which includes from 2 up to 4 cytotoxics with different mechanism of action.

The most wide-spread combinations of polychemotherapy are as follows:

CMF - Cyclophosphan, Adriamycin, Phthoruracil;

CMFP - Cyclophosphan, Adriamycin, Phthoruracil, Prednisolon;

CAF - Cyclophosphan, Adriamycin, Phthoruracil;

CAMF - Cyclophosphan, Adriamycin, Methotrexat, Phthoruracil;
CAV - Cyclophosphan, Adriamycin, Vincristin.

Prognosis

BC treatment prognosis depends on the stage of disease, degree of tumoral cell differentiation, patients age and adequate treatment.

The 5 year survival:

Tis – 3 N0M0 (cancer is limited to the breast) – 97%;

T1 – 3 N1 – 2 M0 (cancer has spread to the regional lymph nodes) – 78%;

Any T Any N M1, Any T N3 M0 (cancer has spread to a distant site)23%.

Questions for self control

1. Risk factors of breast cancer.
2. What are the pathogenetic forms of breast cancer?
3. What are the symptoms of breast cancer?
4. What age is more frequent for development of breast cancer?
5. Give histological classification of breast cancer
6. What are the early methods of diagnoses?
7. Describe the main methods of treatment.

Tests (choose the correct option)

1. Paget's carcinoma is usually an infiltrating carcinoma of:

- a) skin of axillaries;
- b) lymph – nodes;
- c) lung;
- d) breast areola

2. Breast cancer risk factor is:

- a) early first pregnancy;
- b) present in history benign tumors of breast cancer;
- c) early beginning of menstruating and menopause of patients over 55 years.
- d) hypoastrogenemia.

3. What nodal form of BC is most common?

- a) nodal;
- b) diffused;
- c) Peget's disease;
- d) marginal form;
- e) primary – multiple.

4. The most reliable diagnostic test for breast cancer is:

- a) ultrasound;
- b) mammography;
- c) puncture biopsy;
- d) open excision biopsy.

5. Imaging of pulmonary metastases in breast cancer is done by

- a) mammography;
- b) spirometry;
- c) chest radiography;
- d) sputum examination.

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

THYROID CANCER

Incidence

Malignant tumors of the thyroid gland make about 1.3 % among all malignant neoplasms.

Thyroid gland cancer incidence has recently increased significantly in Ukraine. In Ukraine the incidence was 6.6 cases per 100.000 population in 2012 year (in men 2.5, in women 10.1 cases). During last 10 years the case rate of thyroid gland cancer has grown more than 3 times.

Thyroid cancer affects women more often than men and usually occurs in patients 25 - 65 years of age. The high – risk age for well – differentiated thyroid cancer is the 4th or 5th decade.

Risk factors

The etiology of thyroid gland cancer is not clear. Scientists distinguish exogenous and endogenous modifying factors.

Exogenous factors are: radiation exposure, treatment by thyreostatics (especially Mercazolilum), low dietary iodine intake (endemia of struma).

Endogenous factors are genetically caused enzyme defects of hormonopoesis, hormonal infringements in an organism, causing the increased thyrotropic stimulation by a pituitary body, hereditary predisposition to development of “familial form” of the thyroid gland medullary cancer, thyroid gland age involution.

Association between therapeutic irradiation of the head and neck region and the development of thyroid carcinoma has been confirmed by many studies. Risk is the highest among children exposed before the age of 10.

Radiation exposure significantly increases the risk of developing thyroid malignancies, particularly papillary thyroid carcinoma. Radiation targeting the thyroid gland (eg, iodine 131 ablation of the thyroid gland) or high – dose external beam radiation therapy does not appear to increase the risk of papillary thyroid carcinoma.

An increased incidence of thyroid neoplasia from atomic bomb fallout in Hiroshima and Nagasaki has been marked. There was a linear

dose – response relation between distance from bomb blast site and chance of development of thyroid nodules.

Nuclear accidents in Chernobyl in 1986 increase the rate of thyroid cancer.

Radiation increases the risk for thyroid cancer and thyroid nodules.

- Sex (women have increased risk);
- Age (the younger the patient at the time of radiation the greater the risk for subsequent cancer);
- Interval (the more years since radiation the greater chance of cancer);
- Dose (risk for liver from 300 – 1200 Gy).

Chronic thyroid stimulating hormone (TSH) stimulation plays a permissive but not initiative role in the etiology of well – differentiated thyroid cancer.

K – RAS oncogene is associated with radiation - induced thyroid cancer. The RAS and PTC oncogenes play a significant role in pathogenesis. Genetic factors are most important in the genesis of Medullary Thyroid Carcinoma (MTC).

Iodine deficiency may lead to follicular cancer, and iodine abundance is associated with papillary thyroid cancer.

Low dietary iodine intake does not increase the incidence of thyroid cancers overall; however, populations with low dietary iodine intake have a higher proportion of follicular and anaplastic carcinomas.

Adenoma or the nodal struma presents the enlargement of the part of the thyroid gland with formation of the single or plural tumoral units of various sizes. It is considered that in most cases (90%) the patients had thyroid gland cancer secondary to parenchymatous adenoma. Malignant tumors develop from thyroid goiter approximately 10 times more often, than in not changed.

Other causes conducting to development of thyroid gland cancer may be trauma, chronic inflammatory processes (strumitis, thyroiditis), hyperplasia.

Persons with increased risk of the thyroid gland cancer:

- 1) Women, with inflammatory diseases or gynecologic and breast tumor;
- 2) The persons having hereditary predisposition to tumors and dysfunction of endocrine system glands;
- 3) The persons with adenoma or adenomatosis of the thyroid gland, relapsing

- euthyroid goiter in endemic regions;
- 4) The persons who have received therapeutic irradiation of the head and neck region, especially in infancy.

Histological classification

3 types of hormone cells are distinguished in the thyroid gland:

A cells (follicular) thyroid hormone secreting cells.

B cells (Hurthle – Ashkinazy) – serotonin – secreting cells.

C cells (parafollicular) calcitonin – secreting cells.

Follicular carcinoma, papillary adenocarcinoma, undifferentiated (anaplastic thyroid cancer) are derived from the A and B cells. Medullary carcinoma is derived of the parafollicular C cells:

- Papillary adenocarcinoma.
- Follicular carcinoma.
- Medullary carcinoma
- Anaplastic carcinoma (undifferentiated).
- Small cell carcinoma.
- Giant cell carcinoma.
- Lymphoma. } rare
- Sarcoma. }
- Carcinosarcoma.

Clinical presentation

The incidence of thyroid nodules is relatively high in general population, but most nodules are benign. No preoperative test can perfectly differentiate malignant from benign nodular disease. Physical examination characteristics of the nodule are poor predictors of the malignant tumor.

There are no pathognomic symptoms at early stages of the thyroid gland cancer. This cancer refers to visual forms. The neck should be examined for jugular (cervical) or central lymph nodes.

The rapid growth, induration, tuberosity are objective symptoms of cancer development within long – standing abnormal thyroid gland.

At absence of anamnesis the main local symptom is enlargement of the thyroid gland or appearance of a new more dense nodule, sometimes in the form of tumor nodule in one of the thyroid lobes or isthmus.

Pathognomic sign of thyroid gland tumor is its mobility in the process of swallowing.

"Latent" or "occult" thyroid gland cancer (25% of cases) is small (less than 1.5 cm in diameter) and manifests itself by metastasizing into jugular (cervical) lymph nodes, lungs or bones.

In the process of development thyroid gland cancer invades the tumor capsule and extends into the surrounding tissues: invades trachea wall, rarely esophagus, muscles, jugular nervous – vascular bundle.

Local symptoms such as airway obstruction, hoarseness, and dysphagia may be associated with extensive thyroid cancer or goiter.

Papillary adenocarcinoma usually metastasized by the way of lymphatics, and follicular carcinoma metastasizes by blood stream. Regional and distant metastases are observed in females not so often as in males because the former usually have differentiated forms of cancer. Jugular, supraclavicular and later mediastinal lymph nodes are affected by the way of lymphatics.

Pathology

Most malignant thyroid gland tumors are of glandular epithelial origin and are carcinomas. Some well – differentiated thyroid cancers grow slowly, thus the diagnosis depends on blood vessel or capsular invasion.

Papillary thyroid cancer is the most common type of thyroid malignancy in patients older than 45 years.

Papillary cancer is characterized by:

- infiltrative pattern of growth;
- multicentricity;
- spread to regional lymph nodes.

Follicular thyroid cancer occurs less frequently than papillary carcinoma does

- Follicular thyroid carcinoma must be distinguished from follicular adenoma, the distinction is based on the presence or absence of invasion of vessels or the tumor capsule. Patients with follicular cancer have good prognosis but they account for more deaths from

disease than do patients with papillary carcinoma. The 10 – year survival is better for patients with follicular carcinoma without vascular invasion than it is for patients with vascular invasion.

- Follicular carcinomas more commonly have blood vessel invasion and tend to metastasize hematogenously to the lung and to the bone, lymph node metastases are infrequent.
- Follicular carcinoma shows slow growth and good prognosis (if the tumor is small (≤ 4.0)).

Medullary thyroid cancer makes up 5% of all thyroid cancers

- It may occur at any age, but the highest incidence is in the fifth and sixth decades.
- Cytology typically reveals hypercellular tumors with spindle shaped cells and poor adhesion.
- Medullary carcinoma usually presents as a hard mass and it is often accompanied by vessel invasion.
- The overall survival of patients with MTC is 86% at 5 years and 65% at 10 years. Poor prognostic factors include advanced age, advanced stage, prior neck surgery, and associated multiple endocrine neoplasia (MEN) 2B.
- Medullary carcinoma usually secretes calcitonin, a hormonal marker for the tumor, and may be detectable in blood even when the tumor is clinically occult. Metastases to regional lymph nodes are found in about 5% cases.

Anaplastic thyroid cancer makes up 5% of all thyroid cancer

- Undifferentiated (anaplastic) carcinomas grow rapidly and are highly malignant. There may be a greater incidence in countries with endemic goiter.
- Active regional and distant metastasizing is characteristic for anaplastic cancer. Median three – months survival is observed in the patients from the presentation.

Clinical classification of the thyroid gland cancer by TNM system

T – primary tumor

TX – primary tumor cannot be assessed.

T0 – no evidence of primary tumor;

T1 - tumor \leq 2 cm in the greatest dimension thyroid;

T2 - tumor $>$ 2 cm but \leq 4cm in the greatest dimension, limited to the thyroid;

T3 - tumor $>$ 4 cm in the greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension;

T4a - tumor of any size extending beyond the thyroid capsule to invade the subcutaneous soft tissues, larynx, esophagus, or recurrent laryngeal nerve;

T4b - tumor invades the prevertebral fascia or encases the carotid artery or mediastinal vessels.

N - regional lymph nodes:

NX –regional lymph nodes cannot be assessed;

N0 - no regional lymph node metastases;

N1 – regional lymph node metastases;

N1a – metastasis to level VI (the pretracheal, paratracheal and prelaryngeal lymph nodes);

N1b - metastases to unilateral or bilateral cervical or superior mediastinal lymph nodes.

M - remote metastases:

MX – distant metastases cannot be assessed;

M0 – no distant metastases;

M1 - distant metastases.

Grouping of the thyroid gland in stages

Papillary and follicular cancer

Patients under 45 years

Stage 1 - any T, any N, M0

Stage 2 - any T, any N, M1

Stage 3

Stage 4

Older than 45 years

T1 N0 M0

T2 N0 M0

T3 N0 M0

T4 N0 M0any

any T N1 M0

any T any N M1

Medullar cancer

| | |
|-----------|----------------|
| Stage I | T1 N0 M0 |
| Stage II | T2 N0 M0 |
| Stage III | T3 N0 M0 |
| | T1 N1a M0 |
| | T2 N1a M0 |
| | T3 N1a M0 |
| Stage IVA | T4a N0 M0 |
| | T4a N1a M0 |
| | T1 N1b M0 |
| | T2 N1b M0 |
| | T3 N1b M0 |
| | T4a N1b M0 |
| Stage 4B | any T any N M0 |
| Stage 4C | any T any N M1 |

Anaplastic thyroid cancer

- All anaplastic carcinomas are considered stage IV.
- Stage IVA T4a, any N, M0
- Stage IVB T4b, any N, M0
- Stage IVC Any T, any N, M1

Diagnosis

I. History (anamnesis).

II. Head and neck physical examination of jugular (cervical) soft tissues. Thyroid nodules less than 1 cm in diameter are often not palpable. Hard and fixed nodules are more likely to be malignant than soft mobile nodules are. A single palpable nodule is met more often than normal multinodular or diffusely enlarged thyroid gland. Firm cervical masses are highly suspicious for regional lymph node metastases. Vocal cord paralysis implies involvement of the recurrent laryngeal nerve.

II. Thyroid ultrasound.

Patients with palpable thyroid nodules are recommended thyroid ultrasonography.

This method can't distinguish benign from malignant lesions if they are mixed with solid and cystic component or if they are entirely solid.

III. X – ray.

IV. CT scan.

V. Isotope scan (I^{131}) (radionuclide imaging).

VI. MRT.

IV. Biopsy.

- fine needle aspiration biopsy (is the most important diagnostic method in the evaluation of thyroid nodules).

It is recommended to perform at least 3 separate aspirations to minimize false – negative results.

- open biopsy. Solid nodules are excised despite negative cytology.

V. Laryngoscopy (hoarseness, difficulty in swallowing liquids, dyspnea).

VI. Detection of metastatic disease:

- neck ultrasound scan.
- chest radiograph.
- isotope bone scan.

Treatment

Surgery is the basic method of thyroid gland cancer treatment in combination with courses of radioiodine therapy suppressive hormone therapy by L - thyroxin, distant gamma – therapy and chemotherapy. Very often such treatment has good prognosis. Thyroid gland cancer treatment depends on its morphological form and stage of disease.

Preoperative cytologic and intraoperative histological morphological diagnostics of thyroid gland cancer don't always allow to differentiate malignant and benign tumor.

I. Surgery

Surgical resection is performed on the assumption that the nodule represents carcinoma.

1. *Extracapsular total thyroidectomy* – is performed for treating well – differentiated thyroid carcinoma. Total thyroidectomy is surgical removal of all apparent thyroid tissue. Recurrent laryngeal nerve injury and hypoparathyroidism because of inadvertent damage or

removal of the parathyroid glands are the main complication in this procedure.

2. *Subtotal thyroidectomy* – is an alternative to total thyroidectomy. At this procedure a small portion of gross thyroid tissue on the opposite side of malignancy is left to minimize the risk of recurrent laryngeal nerve injury and inadvertent removal of parathyroid glands on that side.

At subtotal thyroidectomy postoperative radioiodine treatment is performed to ablate the remaining thyroid tissue. Additional extensive neck dissection after thyroidectomy is performed (to remove tumor in lymph nodes).

Krayle's operation (extended removal of fats of a neck) is carried out at neck lymph node metastasis.

Usually patients are treated by thyroxine or triiodothyronine after thyroidectomy, but sometimes, the patients with expressed therapeutic pathology, nonresectable tumors are treated only by Iodine¹³¹. (I^{131}).

II. Thyroid suppression therapy (TST)

TST follows thyroidectomy and radioiodine suppression. The purpose of this procedure is to suppress a secretion of thyrotropic hormone by supraphysiological doses of a thyroxine (thyroid – stimulating hormone).

Thyrotropic hormone leads to thyroid gland cells growth at papillary and follicular cancer. Suppression of these hormones reduces risk of relapse in thyroid tissues and probability of the remote metastases.

High doses and long term of thyroxine administration can lead to hyperthyroidism, osteoporosis and infringement of heart function.

It is necessary to administrate substitution therapy in case of complications occurrence.

III. Radiotherapy

External – beam radiation therapy is obligatory for undifferentiated cancer treatment at medullary and thyroid gland squamous cell carcinoma. At papillary and follicular thyroid gland cancer external radiation therapy and chemotherapy are noneffective. At medullary and undifferentiated thyroid gland cancer postoperative external beam radiation therapy is carried out with " decollete" field (neck, top mediastinum) by a single dose 2 Gr, up to achievement of a cooperative dose 40 Gr.

Radiotherapy is used for treatment the patients with localized lesions that are unresponsive to ^{131}I .

Radiotherapy may be used in patients, who are not surgical candidates.

IV. Chemotherapy

Complete responses to chemotherapy are rare (pappilary, follicular, medulary thyroid carcinoma).

- 1) Nonresectable, medullary or undifferentiated forms, fast – growing recurrent tumors, distant metastases an undifferentiated cancer after operation are indications to chemotherapy.
- 2) The combination of doxorubicin and cisplatin appears to be more active than doxorubicin alone.

Anaplastic thyroid cancer treatment with drugs has been reported to produce partial remissions in some patients. 30% of patients achieve a partial remission with adriamycin. Palliative chemotherapy has been reported to produce occasional responses in patients with metastatic diseases. There is no single drug regimen which can be considered standard. Standard regimens are CAV (cyclophasfan, doxorubicin, vincristine), BAV (bleomycin, doxorubicin, vincristin).

V. Postoperative radioiodine scanning and ablation.

Radioiodine will preferentially target residual normal or malignant tissue after thyroidectomy, because differentiated thyroid tissue and well – differentiated thyroid carcinomas are TST sensitive and will take up iodine. Thus, radioiodine can be given in diagnostic doses to detect residual normal or neoplastic tissue in the body and in therapeutic doses to ablate this tissue.

After thyroidectomy patients undergo thyroid replacement therapy (thyroxine or triiodothyronine). ^{131}I scanning is performed when the patient is in a hypothyroid state (TSH > 50).

A promising new development for follow – up thyroid scanning is the use of recombinant human TSH as opposed to withdrawing T4 to increase autogenous TSH levels.

Prognosis

- 1) Prognosis depends on patient's age, sex, histologic grade, and type of surgical resection.

- 2) The overall 5 – year survival rate is less than 10%, and most patients do not live longer than a few months after diagnosis.
- 3) The 10 year survival for:
 - papillary cancer – 93%;
 - follicular cancer – 85%;
 - medullary cancer – 75%;
 - undifferentiated anaplastic cancer – 14%.
- 4) The 20 year survival for:
 - low – risk patients – 98%;
 - high – risk patients – 50%.

Questions for self control

1. Where is the lowest incidence of thyroid cancer in the world?
2. What histologic types of TC are known?
3. Methods of diagnosis.
4. What are the factors of TC?
5. What kind of thyroid cancer is radically treated by radiotherapy?

Tests (choose the correct option)

1. Regional lymph nodes for thyroid gland cancer are:

- a) jugular and paratracheal
- b) retrosternal
- c) axillary
- d) submandibular
- e) subclavicular

2. Punction biopsy with cytology is effective in:

- a) 95% of cases
- b) 60% of cases
- c) 48% of cases
- d) 30% of cases
- e) 15% of cases

3. Risk factors of thyroid gland carcinoma:

- a) alcohol abuse
- b) smoking
- c) exposure to radiation
- d) obesity
- e) chemical irritants

4. Peak incidence of thyroid cancer

- a) 25 years
- b) 60 years
- c) the fourth and fifth decade of life
- d) the third decade of life

5. What kind of thyroid cancer is found more often?

- a) squamous cell carcinoma
- b) follicular carcinoma
- c) papillary carcinoma
- d) medullary thyroid carcinoma

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

SKIN TUMORS

Skin cancers (Basal cell carcinoma – BCC and squamous cell carcinoma – SCC).

Skin consists of three layers: epidermis, dermis, and hypodermis (subcutis).

Ketzo described skin cancer forms in 1790.

Incidence

Constantly increasing incidence of malignant skin neoplasms all over the world is called "quiet epidemy". Malignant skin diseases account for approximately 25% of all malignant tumors.

Basal cell carcinoma is the most frequently diagnosed skin cancer in whites 75 – 80% of reported cases. *Squamous cell carcinoma* is the second most common skin cancer (20% to 25% of all reported skin cancer cases).

Sex – men are affected twice as often as women.

Age – basalioma is rarely found in patients younger than 40 years.

Race – basalioma is most often found in light – skinned persons.

Death rate is very low, less than 0.1%.

In Ukraine the incidence of skin cancers was 44.5 cases per 100000 population in 2012 year (in men 39.7, in women 48.7 cases).

Basal cell carcinoma – is the most common cutaneous malignancy in humans.

It may originate from epithelial cells of hair follicles. Thus it is rare on the vermilion border of the lip, external genital organs. BCC can invade underlying tissues and organs slowly and cause destruction of skin, cartilage, soft tissue and bone. If BCC reaches the bone or blood circulation (which happens rarely) it may metastasize

BCC is very dangerous when it is localized on eye lids, the nosolobial fold, auricle. After it reaches metastatic levels it behaves aggressively as other types of cancers and can spread to vital organs such as lymph nodes and lungs.

Risk factors

- Other primary malignancies.
- Exposure to ultraviolet radiation (UV light affects the host immune system).
- Long – term contact with chemical carcinogens – products of oil refining, coal, shale oils, arsenic combinations.
- Traumatic skin injuries (mechanical injuries, burns).
- Exposure to artificial light (tanning booths, light therapy)
- Sex. Basal cell carcinoma occurs more commonly in men than in women (2:1).
- Age. Basalioma is rarely found in patients younger than 40 years. Its incidence increases with age. It is usually seen in elderly persons.
- Race. Basalioma is most often found in light – skinned persons.
- Viruses (HPV).
- Host immunity.
- Persons with outdoor occupations (sailors and farmers).
- Genetic factors (genodermatoses).
- Ionizing radiation.

Ionizing radiation received as part of therapeutic modalities can promote the development of BCC.

X – radiation was used for the treatment of acne and hypertrichosis. Many patients who received therapeutic X – rays developed radiation dermatitis and multiple skin cancers of the face 20 to 30 years later. UV light affects Langerhans cells in human skin, which may alter the host immune system, allowing the development and progression of skin cancer.

Pathomorphology

Basal cell (basalioma) – 70%;
Squamous cell carcinoma – 30%.

BCCs are masses of basaloid cells resembling cells in the basal layer of epidermis extending down from the epidermis into the dermis.

Precancerous forms

Benign tumors rarely give rise to malignant tumors but they may be confused with some of the malignant lesions. Benign tumors should be differentiated from malignant skin tumors.

Facultative forms

Cutaneous (skin) horn.

Keratosis.

Senile skin atrophy.

Ateroma.

Deep skin mycosis.

Papilloma.

Keratoacanthoma (It is difficult to differentiate between keratoacanthoma and squamous cell carcinoma. Keratoacanthoma behaves more aggressively in immunosuppressed hosts).

Red flat herpes.

Obligate forms

Bowen's disease (intraepidermal carcinoma in situ).

Xeroderma pigmentosum.

Cair disease.

Fistula.

Scars.

Chronical ulcer.

Trauma.

Burns.

Classification of non – melanoma skin cancers by TNM system

Primary tumor

TX – not enough evidence for the primary tumor.

T0 - the primary tumor is not indentified

Tis – carcinoma in situ.

T1 – the tumor is 2 cm in the greatest dimension.

T2 – the tumor is >5 cm, but < 5 cm in the greatest dimension.

T3 – the tumor is >5 cm in the greatest dimension.

T4 – the tumor grows into the lower organs (cartilages, muscles, bones).

Regional lymph node involvement

NX – not enough evidence for regional lymph nodes evaluation.

N0 – no evidence of regional lymph nodes affected.

N1 – the regional lymph nodes are affected.

Metastatic involvement

MX – not enough evidence to identify distant metastasis.

M0 – distant metastasis is not identified.

M1 – there is distant metastasis.

Grouping of non – melanoma skin cancers in stages

Stage 0 - TisN0M0

Stage I – T1N0M0

Stage II – T2N0M0

T3N0M0

Stage III– T4 N0 M0 or any T N1 M0

Stage IV – any T, any N, M1

Clinical presentation (Fig. 27, 28, 29). Physical signs.

BCC is a slowly growing, shiny, skin – colored to pink, translucent, raised papulae. As the lesion enlarges it may ulcerate and develop a rolled border and crusted center. The lesion may then regress to a smaller size.

Classification (clinical forms)

1. Nodular basalioma is the most common type of BCC. (round, flesh – colored). As it enlarges it frequently ulcerates centrally. It observed on the face, but trunk and extremities can be also affected.
2. Pigmented basalioma – may be confused with malignant melanoma. It has brown black macules in some or all areas. Typically some areas of these tumors do not retain pigment.
3. Sclerosing basalioma (morphea – type BCC has a scar – like sclerotic appearance and lacks telangiectasia and translucency) – white or yellow, waxy, sclerotic plaque, that rarely ulcerates.
4. Superficial basalioma – appears as an erythematous, often with whitish scale. (multicentric).

5. Fibroepithelioma of Pinkus is a very rare form of BCC. It is usually seen on the back and appears as flesh colored skin tags, a network of anastomosing epithelial strands connected to the overlying epidermis and admixed with a fibrous stroma. The network may be a few layers thick.



Fig. 27. Head skin cancer.



Fig. 28. Hand skin cancer



Fig. 29. Skin cancer

Diagnosis

- History (anamnesis).
- Examination.
- Palpation.
- Dermatoscopy.
- Cytological analysis of the scrape, smear.
- Histologic examination (incisional biopsy for histologic confirmation).
- Sonography (to diagnose metastases in regional lymph nodes).
- X ray. Radiography of the thoracic cavity organs.
- Abdominal cavity ultrasonography.

Differential diagnosis

Tuberculosis.

Red Lupus.

Actinomycosis.

Syphilitic gumma.

Melanoma.

Epidermal nevi.

Kyrle's disease.

Squamous cell carcinoma (SCC)

SCC is a malignant skin cancer arising from epidermal Keratinocytes with the potential for metastasis. SCC accounts for 20% of all malignant tumor neoplasms. Precancer disease: chronic ulceration, chronic sinus disease, chronic inflammation, and scar tissues increase the chance of developing SCC, because agents used for the chronic skin conditions are carcinogenic and may cause SCC.

Differential diagnosis (SCC)

- keratoacanthoma;
- spinal cell melanoma;
- soft tissue sarcoma with spindle cells;
- Bowen's disease;
- erythroplasia of Queyrat;
- solar keratosis;
- large cell acanthoma;
- chondrodermatitis nodularis Helicis.

Clinical presentation

Clinical presentation of squamous cell carcinoma appears on the areas of the skin damaged by sun exposure. The most common sites of SCC are

- face;
- neck;
- chest;
- back;
- palm;
- sole;
- dorsum of the hand of an elderly white patients with sun – damaged skin.
- periauricular area, postauricular area, the paranasal area, nasolobial fold, inner canthal areas.

The primary lesion is red, indurated papule that appears de novo or on an actinic keratosis and expands rapidly, producing a large nodule that eventually ulcerates and metastasizes to a local draining lymph node.

Precursor sites of SCCs are: Bowen's disease, cutaneous horn, chondrodermatitis nodularis helices, chronic ulcers, scar tissue and radiodermatitis.

SCC of mucocutaneous site usually occurs in patients with a history of heavy smoking and heavy alcohol intake.

Chewing tobacco can cause the development of oral squamous CC. Verrucous carcinoma may occur in oral cavity or sole of the foot (persistent, firm or vegetating, plaque).

Giant condylomata of Buschke – Lowenstein (wart-like lesions on the male genitalia).

Epithelioma cuniculatum (a small ulcer with peripheral hyperkeratosis on the soles of the feet).

Treatment

Similar treatment modalities are used for basal cell carcinoma and squamous cell carcinoma.

After histologic diagnosis confirmation some factors should be considered to determine the appropriate therapeutic approach. The size of the lesion, the anatomic location, the clinical nature, histologic characteristics, general health and age of the patient, and whether the lesion is primary, recurrent, or metastatic should be considered. All these factors play an important role in the final outcome of the treatment.

For high – risk areas should be selected the type of treatment that gives the highest cure rate and least chance of recurrence, such as Mohs' micrographic surgery.

Mohs' micrographic surgery (microscopically controlled excisional surgery) allows the removed tissue to be mapped in relation to the underlying site. Additional tissue removal is carried out at sites where tumor cells are present microscopically. The treatment is considered complete when there is no tumor found in removed tissue. Mohs' surgery has a cure rate of 96% to 99%.

Cryosurgery

Cryotherapy can be used for the treatment of lesions smaller than 2 cm that are located on the eyelid, ear, chest, back, or tip of the nose. Tumor located on the nasolabial fold or inner canthal require wider margins of

freezing to increase the cure rate. It is recommended for the treatment of recurrent tumors and tumors with definable margins T1-2N0M0. A 5 to 10mm tumor – free margin is used to increase the cure rate. Not less than triple freeze – thaw cycle is required for safe and accurate treatment. Cryotherapy cannot be used in patients with abnormal cold intolerance. Cryotherapy takes advantage of the cryonecrosis that is achieved by cellular and microvascular response to subzero temperatures. This therapy gives good cosmetic results.

Radiation therapy is recommended for patients who are poor surgical risks or are elderly debilitated or when the tumor is large.

Closely – focused radiotherapy can be used alone for treatment of skin cancers. Most skin cancers are radiosensitive. Closely – focused radiotherapy (Stage I,II) total dose is 30 – 60 Gr.

The goal of radiation is to selectively destroy the tumor tissue and spare the normal surrounding area. Modern radiologic technology has made it possible to select the quality, dose, and fractionation of the radiation so that only the neoplastic tissue is destroyed.

Photodynamic therapy has been used in the skin cancer treatment. Photosensitizing substance is injected and selectively retained by the malignant tumor but not by normal tissue. After exposure to penetrating visible light, the photosensitizing substance undergoes photodynamic activation and destroys the tumor cells and spare the surrounding normal skin. (hematoporphyrin derivatives and red laser light with a wavelength of 600 to 700 nm).

Chemotherapy. Cysplatin, adriamicin, bleomicin, give good effect (total or part regression).

Prognosis

5 year survival:

Stage I – 100%;

Stage II – 86%;

Stage III – 62%;

Stage IV – 12%.

Melanoma

Melanoma accounts for only 4% of all skin cancer.

Incidence

The incidence of melanoma has been increasing steadily at a rate faster than that for any other cancer among white populations throughout the world, may be because of earlier detection of melanoma or increased recreational exposure to sunlight. High incidence of melanoma is observed in a fair – skinned population and low incidence for e.g. in China. In Ukraine the incidence of melanoma was 6.8 cases per 100000 population in 2012 year (in men 6.0, in women 7.5 cases).

Risk factors

Exogenous risk factors

- **Physical factors:** a fair complexion, tendency to sunburn rather than tan even after a brief exposure to sunlight. Ultra – violet solar radiation, ionizing radiation, fluorescence radiation; pigmented nevus.
- **Chemical factors:** harmful chemical agents used in petrochemical, chemical (producing nitric acid), rubber – producing plants, in the production of vinyl chloride, polyvinyl chloride, plastic, benzol, pesticides.
- **Biological factors:** dietary factors, medical drugs (exogenous estrogens).

Endogenous risk factors

- Pigmented xeroderma.
- Race and ethnic predisposition.
- Malignant melanoma: Dubrei melanosis, nevi.

Genetic factors

- Dysplastic nevus syndrome.
- Patients having > 20 nevi have threefold increase in risk.
- Xeroderma pigmentosum.
- Bazex's syndrome.
- Torre's syndrome.
- Cowden's syndrome.

- Gardner's syndrome.
- Peutz – Jeghers syndrome.
- Carney's syndrome.
- Dyskeratosis congenital.
- Multiple self – healing epithelioma of Ferguson – Smith.
- Basal cell nevus syndrome.

Pathomorphology

- Epithelial.
- Spindle – cell.
- Mixed.
- Small – cell.

Histopathologic forms of melanoma

The four major growth patterns are:

- Superficial spreading melanoma (SSM) (70%) arises in a pre-existing nevus (deeply pigmented area in a brown junctional nevus). It may be found on any body surface, especially head, neck, and trunk of males and the lower extremities of females. SSM can occur at any age after puberty.
- Nodule – like (nodular 15%)
Nodular melanomas (NMs) are found on any body surface but most common on the trunk or head or neck. They are the most symmetrical and uniform of the melanomas, are dark brown or black in colour, and more raised or dome – shaped. NM_s are more aggressive tumours and usually develop more rapidly than SSM_s (2% - 8%).
- Acral lentiginous and mucous melanoma. (ALMs). They are found on palms, beneath the nail beds, soles). Generally large tan or brown flat stains often resemble Lentigo maligna melanoma (LMH_s).
- Lentigo maligna melanoma (LMMs) 4 – 10% – they occur on sun – exposed areas (back of the hand, face, neck) in older white women. Generally large (>3mm), flat lesions that occur in an older age group (after 50 years).

Classification of melanoma skin cancer by TNM system

Primary tumor

- Tis – melanoma in situ.
- T1 – the tumor is less than 1 mm thick: a) without ulceration and the invasion level is II/III; b) with ulceration or the invasion level is IV/V.
- T2 – the tumor is 1.01 – 2.0 mm thick: a) without ulceration; b) with ulceration.
- T3 – the tumor is 2.01 – 4.0 mm thick: a) without ulceration; b) with ulceration.
- T4 – the tumor is more than 4 mm thick: a) without ulceration; b) with ulceration.

Regional lymph node involvement

- N1 – metastases in 1 gland: a) micrometastases 1; b) micrometastases 2.
- N2 - metastases in 2 - 3 lymph nodes: a) micrometastases 1; b) micrometastases 2; c) transitional metastases/satellites without metastatic lymph nodes.
- N3 – 4 and more metastatic lymph nodes or a conglomeration of lymph nodes, or transitional metastases/satellites with metastatic lymph nodes.

Micrometastases 1 are diagnosed after observation or selective lymphodenectomy.

Micrometastases 2 are clinically found in lymph nodes, confirmed by therapeutical lymphodenectomy or extracapsular spread of metastases in the lymph nodes.

Metastatic involvement

M1a – there are distant metastases on the skin, hypoderma or in the lymph nodes.

M1b – metastases in the lungs.

M1c – other visceral or any distant metastases.

Grouping of skin melanoma stages

| | Clinical stages TNM | Morphological stages_p TNM |
|------------|-------------------------------|--|
| Stage 0 | Tis N0 M0 | Tis N0 M0 |
| Stage IA | T1a N0 M0 | T1a N0 M0 |
| Stage IB | T1b N0 M0 | T1b N0 M0 |
| | T2a N0 M0 | T2a N0 M0 |
| Stage IIA | T2b N0 M0 | T2b N0 M0 |
| | T3b N0 M0 | T3a N0 M0 |
| Stage IIB | T3b N0 M0 | T3b N0 M0 |
| | T4a N0 M0 | T4a N0 M0 |
| Stage IIC | T4b N0 M0 | T4b N0 M0 |
| Stage III | Any T N1 M0 N2 M0 N3 M0 | |
| Stage IIIA | | T1-4a N1a M0 T1-4a N2a M0 |
| Stage IIIB | | T1-4b N1a M0 T1-4b N2a M0 T1-4a N1b M0 T1-4a N2b M0 T1-4a/b N2c M0 |
| Stage IIIC | | T1-4b N1b M0 T1-4b N2b M0 Any T N3 M0 |
| Stage IV | Any T Any N Any M1 | Any T Any N Any M1 |

Breslow's staging

The Breslow microstaging method measures the thickness of the lesion using an ocular micrometer.

Less than or equal to 0.75 mm

0.76 – 1.5 mm

1.51 – 4 mm

Greater than or equal to 4 mm.

Clark has proposed a model of tumor progression for melanoma. His model defines lesions that represent putative steps in progression from normal melanocyte to melanoma. Lesions range from benign to most

malignant in the following progression:

common acquired → dysplastic nevus → primary melanoma (superficial or radial growth phase) → primary melanoma (deep or vertical growth phase) → metastatic melanoma.

Normal melanocytes require exogenous growth factors for proliferation.

Melanoma cells can grow in the absence of any exogenous growth supplements, suggesting that they produce their own growth factors.

The Clark microstaging method categorizes levels of invasion that reflect increasing depth of penetration into the dermal layers (Fig. 30).

Clark's staging

Level I – All tumor cells above basement membrane (in situ)

Level II – Tumor extends into papillary dermis

Level III – Tumor extends to interface between papillary and reticular dermis

Level IV – Tumor extends between bundles of collagen of reticular dermis

Level V – Tumor invasion of subcutaneous tissue

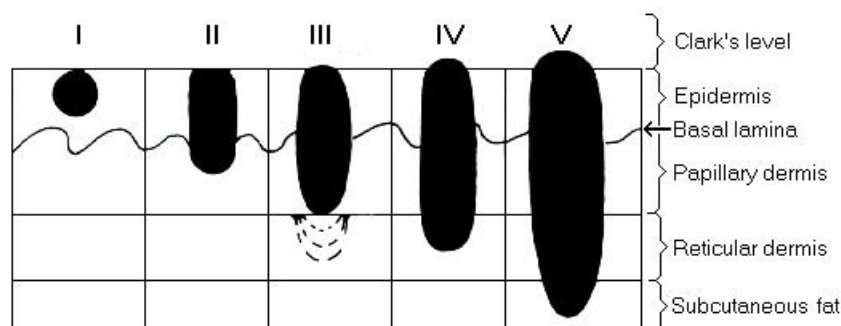


Fig. 30. Clark's staging

Clinical presentation(Fig. 31, 32, 33)

- Asymmetry (melanoma lesion is more likely to be asymmetric)
- Colour (melanoma is more likely to be very dark black or blue and have variation in colour than a benign mole, which more often is uniform in colour and light tan or brown).
- Horizontal and vertical growth of the nevus melanoma.
- Unpleasant sensation of heat, itching or pain in the nevus surface.
- Absence of hair on the nevus surface.

- Nevus is depigmented in the old age.
- Ulceration of the epidermis above the nevus melanoma.
- Appearance of single nodules (satellites) around the nevus.
- Peeling of the nevus surface with formation of withered "scabs".
- Consistence change of the nevus – melanoma (detected by palpation), its softening.
- Weeping of the nevus – melanoma surface.
- Bleeding of the nevus – melanoma.
- Lymph nodes enlargement.
- Border irregularity.

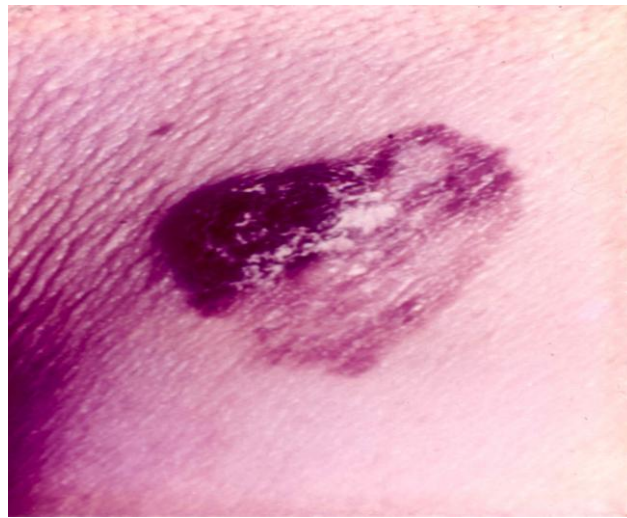


Fig. 31. Lentigo maligna melanoma.

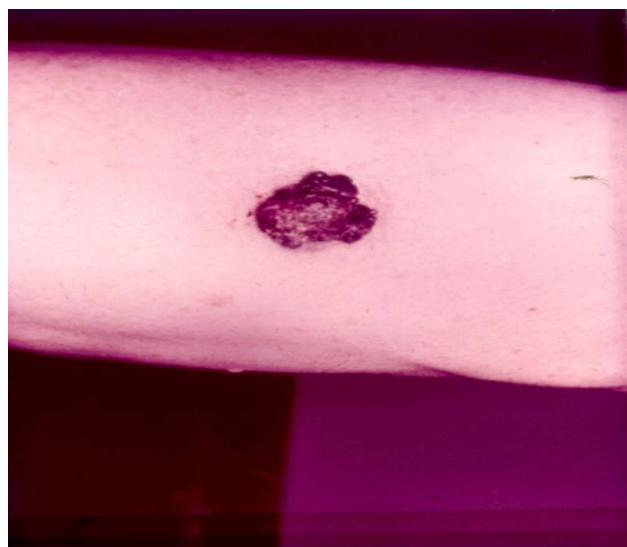


Fig. 32. Forearm superficial spreading melanoma.



Fig. 33. Shin nodular melanoma.

Diagnosis

- Examination of the scalp, ears, palms, soles, mucous membranes, regional lymph nodes palpation;
- Anamnesis (duration of the lesion, associated symptoms (pain, itching), occupational, recreational history, prior sun exposure history of arsenic ingestion, chronic ulcer, burn scar osteomyelitis; family history of cancers.
- Dermatoscopy.
- Echography.
- Cytological analysis of smears (of ulcerated tumor) – tumor prints (any biopsy except tumor prints of weeping nevus must not be done).
- Sentinel node biopsy.
- Osteoscintigraphy.
- Radioisotope scanning with the help of radio – active ^{32}P (300%).
- Chest X – ray.
- CT scan or MRI of brain.
- US.

Differential diagnosis

Youth melanoma (pits nevus).

Blue nevus (dysplastic nevus syndrome (10 to 100 pigmented lesions)

Galo – nevus.

Displastic nevus.

Cavernous thrombotic gemangioma.

Non – malignant skin tumors.

Malignant skin tumors.

Underungual and underepidermal hematoma.

Onihomikosis.

Extragenital chancre.

Metastases of tumors of other histogenesis into skin.

Skin melanoma treatment

Method of melanoma treatment depends on the pattern of its growth and the stage of disease.

Surgery

Patients with stage I and II (T1, T2, N0, N1a) are indicated surgical treatment. Skin excised with 4 cm margins. Tumor is excised unblock with subcutaneous tissue up to aponeurosis or fascia of underlying muscle. When melanoma is located on the finger or on a toe an amputation of the digit is indicated.

After melanoma excision there are great skin defects. Which can be closed with different kinds of skin plasty. On extremities plasty with free skin flaps is used. Primary skin closure is indicated in patients with head, facial, sole of the foot, and palm melanomas.

Prophylactic lymph node dissection lymphadenectomy is indicated at IV – V levels of invasion, if diagnoses of melanoma histologically confirmed.

Different kinds of operations on lymphatic vessels depend on the primary melanoma localization. Patients with melanoma of the lower extremities undergo Dyukan's operation (removal of subcutaneous tissue with groin lymph nodes). Patients with head and neck melanomas undergo Krayl operation. In patients with upper extremities melanomas subcutaneous tissue and axillary lymph nodes are removed.

Radiation therapy

Most melanomas are radioresistant. It can't be indicated alone for primary tumor or regional metastases treatment.

Preoperative closely locus irradiation is indicated in patients with stage III. Single dose is 300 – 500 rad. Distant γ – therapy total dose 40

– 45 Gr of the nearest lymph node metastasizing zones is done simultaneously with primary focus irradiation.

Chemotherapy

Patients with generalized forms of melanoma are treated by chemotherapy. Intra-arterial infusion of dacarbazine can reduce tumor burden.

Partial response rate of decarbasin, in combination with cisplatin, carmustine and tamoxifen is 50%.

Fotomustin and taxenes are used in chemotherapy.

Combinations of polichemotherapy biologic agent (interferon and IL – 2 have been stated).

Immunotherapy

There is evidence that the immune system can influence the pathogenesis of melanoma. Several biologic agents have demonstrated antitumor activity.

1) Interleukin – 2;

2) Monoclonal antibodies treatment of melanoma activate the host immune system;

3) Tumor vaccines induce active immunity against tumors.

Prognosis

10 year survival:

Stage I – 80%;

Stage II – 50%;

Stage III – 25%;

Stage IV – 10%.

Women have a better survival rate than men. The melanomas occurred more commonly on the extremities (a more favorable prognostic site) and were not usually ulcerated. The level of invasion is a significant prognostic factor.

The measurement of tumor thickness is a more accurate prognostic factor. Patients with SSM and LMM lesions have the best survival rate, whereas those with NM lesions have the worst (because the former are

thinner lesions). Patients with systemic metastases (stage IV) have poor prognosis.

Questions for self control

- 1.Name nonmelanoma skin cancers.
- 2.Skin cancer risk factors.
- 3.Precancerous forms of skin cancers.
- 4.Skin cancer TNM classification.
- 5.Clinical presentation of BCC.
- 6.Clinical presentation of SCC.
- 7.Clinical presentation of melanoma.
- 8.Diagnoses of melanoma.
- 9.Melanoma treatment.

Tests (choose the correct option)

1. The most common cutaneous malignancy in humans is

- a) mixed carcinoma;
- b) basal cell carcinoma;
- c) squamous cell carcinoma;
- d) metatypic carcinoma;

2. Factors that can cause skin cancer:

- a) insolation;
- b) thermal burns;
- c) radioactive irradiation;
- d) pigmental xeroderma;
- e) all above mentioned;

3. Morphologic diagnoses of melanoma is:

- a) aspiration biopsy;
- b) incisional biopsy;
- c) excisional biopsy;
- d) tumor prints;

4. The greatest number of skin cancer – related deaths worldwide is associated with

- a) melanoma;
- b) basal cell carcinoma;
- c) squamous cell carcinoma;
- d) Kaposi's sarcoma;

5. A shave biopsy in melanoma is

- a) indicated;
- b) strongly indicated;
- c) compulsory procedure;
- d) contraindicated.

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

MALIGNANT LYMPHOMAS

I. Hodgkin's lymphoma (Lymphogranulomatosis)

II. Non - Hodgkin's malignant lymphoma

This group of diseases includes lymphatic tissue neoplasms, which are characterized by local malignant tumor growth.

Tumor vegetation most often arises in lymphatic nodes however other primary localizations of tumors are possible (spleen, tonsils, gastrointestinal tract).

I. Hodgkin's lymphoma

Incidence of lymphogranulomatosis in Ukraine was 2.7 cases per 100.000 population in 2012 year (in men 2.7, in women 2.8 cases).

Risk factors

Malignant lymphoma etiology, including lymphogranulomatosis is still unclear. There are many theories of lymphogranulomatosis origin: infectious, viral and tumor origin. Clinical picture of disease (alternating temperature, profuse sweat, neutrophil leukocytosis, erythrocyte sedimentation rate (ESR) elevation, lymphoid tissue systemic lesion, typical granuloma formation by analogy with tuberculosis development, lues and other diseases development indicates infectious – inflammatory nature of lymphogranulomatosis. One of the theories runs that Epstein – Barr virus can be the reason of disease.

Existence of Reed - Berezovsky – Shternberg cells or their precursor - Hodgkin's cells in aspirates is evidence of lymphogranulomatosis. Reed - Berezovsky – Shternberg cells are characterized by big size, multiple and different in form nuclei (round and oval), with delicate and evenly disposed chromatin. Cytoplasm is light and wide.

Hodgkin's cells are also large but have only nucleus. Nucleus structure is the same as in Reed - Berezovsky – Shternberg cells. It is established that Hodgkin's and Reed - Berezovsky – Shternberg cells originate (in 80% of cases) from mature slowly profiling B – lymphocytes of germinal center follicle of lymph nodes. 20% of cases are derivatives (off springs) of T – cell line of cytotoxic lymphocytes and maybe derivatives of natural killers.

It is supposed that viruses (in particular Epstein – Barr virus) can block the apoptose process and so pathological in Reed - Berezovsky – Shternberg cells avoid programmed death.

Pathomorphology

There are 4 histologic variants of this disease according to lymphogranulomatosis histologic classification worked up by Lukes and co - authors in 1963 and approved at international symposium in 1965 :

- 1) **Lymphoid – histiocytous** (lymphocyte predominant) variant (15% of Hodgkin's disease) is characterized by lymphocyte and partly by histocytes proliferation.
- 2) **Nodular sclerosis variant** (40 – 50 % of all cases) is characterized by vegetation of fibrous cords which divide lymph node tissue on separate sites in which can be met not numerous Berezovsky – Shternberg cells, neutrophil granulocytes and histocytes. There are two histologic features that differentiate this form of Hodgkin's disease from all others. The first is: Reed – Sternberg and lacunar cells. Lacunar cells are bigger, polynuclear, their cytoplasm is clear and foamy.
- 3) **Mixed cellularity** variant (30% of cases) is presented by cell polymorphism (Reed - Berezovsky – Shternberg cells are available) in combination with marked fibrosis.
- 4) **Lymphocyte depleted** variant Hodgkin's disease (LDHD) accounts for only 5% of all patients has prevalence of atypical reticular cells and Reed - Berezovsky – Shternberg cells presenting focus of necrosis and fibrosis and reduction of lymphocytic number (lymphoid cachexia).

Transition from the stage of lymphocytes predominance to the stage of lymphoid cachexia can be observed.

Staging of malignant lymphoma

Staging systems are anatomic descriptions that describe sites of tumor involvement in relation to the diaphragm.

4 stages of disease are distinguished according to lymphogranulomatosis international classification approved in 1971 in Ann – Arbore.

Patients were classified only by the extent of lymph node involvement (stages I – III) followed by the subscript E, which denoted

direct extension. Involvement of the spleen is indicated by the subscript S. In all systems, patients are classified as A or B on the basis of the absence or presence of constitutional symptoms, such as fever higher than 38⁰C for 3 consecutive days, night sweats, or unexplained loss of more than 10% of body weight in the prior 6 months.

In 1989, a new classification was proposed, known as the Cotswald system. It was developed because of increasing use of new diagnostic techniques such as CT, scanning and magnetic resonance imaging (MRI) and because of the greater appreciation of the influence of tumor bulk as a separate prognostic indicator within any given stage.

The Cotswald Staging Classification (1989) for Hodgkin's disease
(Modified Ann – Arbor classification 1971)

Stage I. Involvement of a single lymph node region or a lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)

Stage II. Involvement of two or more lymph node regions on the same side of the diaphragm (i.e., the mediastinum is a single site, hilar lymph nodes are lateralized). The number lymph nodes are lateralized). The number of anatomic sites should be indicated by a subscript (e.g., II₂).

Stage III. Involvement of lymph node regions or structures on both sides of the diaphragm:

Stage III₁: With or without splenic hilar, celiac, or portal nodes.

Stage III₂: With paraaortic, iliac, mesenteric nodes.

Stage IV. Involvement of extranodal site(s) beyond that designated E:

A: No symptoms

B: Fever, drenching sweats, weight loss

X: Bulky disease:

>1/3 the width of the mediastinum

>10cm maximal dimension of nodal mass

E: Involvement of a single extranodal site, contiguous or proximal to a

known nodal site

CS: Clinical stage

PS: Pathologic stage

Clinical presentation

Local enlargement of lymph nodes (most often cervical, then axillary and inguinal lymph nodes) are the early symptoms of these disease. These lymph nodes have elastic consistence, painless to the touch and they are not fused with surrounding tissues. Then metastases spread to other lymph nodes mainly along lymph ways. At more late stages lymph nodes are multiple, have different size and density depending on remoteness of their lesion. Lymph nodes often fuse in to massive conglomerations.

Other organs are affected in the process of generalization. Increasing intoxication (fever, perspiration, itch, weakness, weight loss and pain in joints) is observed in the process of generalization.

Fever at LGM can be of deferent kin. Daily short term temperature rise is noted very often. It starts with chill and finished witch profuse night sweat, but the patient usually never surfers it. Almost all patients suffer perspiration. Profuse nigh sweat, and high temperate indicate that the disease is very severe.

Pruritus is noted in 25 – 35% of patients.

Itch can be of different degree from moderate to painful itch. The latter prevents the patient from possibility to sleep, causes loss of appetite and nervous breaks.

Weight loss is noted at severe aggregate and at the terminal stage of disease.

Pleura and lungs lesion is usually caused by the process spreading from mediastinum and lung roots lymph nodes. Digestive tract (mucous membrane erosion and perforation, mesenteric lymph nodes enlargement, intestinal obstruction); bones (destructive change, most often in back bone, ribs, sternum, pelvis) can be affected in patients with lymphogranulomatosis. Kidneys function changes are also possible as the result of their lymphogranulomatosis infiltration, amyloidosis development is also possible.

Liver is involved in the process predominantly at the terminal stage of disease – toxic hepatitis or obstructive jaundice arise in the result of fine biliary ways squeezing by sclerosis granulation tissue or universal bile duct obturation by lymph nodes in the liver hilus. Eruption and dermatitis are possible.

Blood changes are manifested in moderate neutrophil leukocytosis with nucleus shift to the left, absolute and relative lymphopenia

(especially at the peak of disease as the result of lymphoid tissue lesion by granulomatosis process), eosinophilia and monocytosis. Leucopenia is noticed at abdominal forms, which cause spleen affection. Anemia usually develops at the late stages of disease. Trombocyte quantity rise (10 – 15% of patients), erythrocyte sedimentation rate increase, fibrinogen concentration augmentation $> 5\text{g/l}$; $\alpha - 2$ globulin $> 10\text{ g/l}$; haptoglobin $> 1,5\text{ mg/l}$ are possible at the peak of this disease.

Involvement of the skin, subcutaneous tissue, and breast can occur with Hodgkin's disease. Unlike other malignant lymphomas, Hodgkin's disease rarely arises in the gastrointestinal tract. Compression of the ureters from lymphadenopathy may occur. Unusual urologic complications of Hodgkin's disease are lipoid nephrosis and amyloid nephrosis, which may occur although no other clinical manifestations of persistence or recurrence are detected.

Diagnosis

Hodgkin's disease usually arises in lymph nodes. The initial diagnosis of Hodgkin's disease can only be made with a biopsy.

Lymphogranulomatosis is proved after open biopsy of affected lymph node in case Reed - Berezovsky – Shternberg cells are revealed in the slide.

Examination of organs and systems is necessary to prove the stage and localization of the process:

- 1) A detailed history (duration and presence or absence of fever, unexplained sweating and its severity, unexplained pruritus, and unexplained weight loss).
- 2) Surgical biopsy.
- 3) Detailed physical examination (attention to all nodebearing areas, including Waldeyer's ring and determination of liver and spleen size).
- 4) Laboratory procedures:
 - a) Complete blood count, including erythrocitic sedimentation rate.
 - b) Evaluation of renal function.
 - c) Evaluation of liver function.
- 5) Radiologic studies
 - a) Chest radiograph (posteroanterior and lateral).
 - b) Chest and abdominal Computed Tomography Scan.

- c) Bilateral lower – extremity lymphogram.
 - d) Views of skeletal system to include thoracic and lumbar vertebral, the pelvis, proximal extremities, and any areas of bone tenderness. US examination of liver, spleen, kidneys, retroperitoneal and intraperitoneal lymph nodes.
- 6) Bone marrow hemopoiesis state assessment (sterna puncture findings and trepan biopsy findings) as well as bone radioisotope examination and roentgenography are of great importance;

Differential diagnosis

Differential diagnosis is necessary in patients who have diseases causing enlargement of lymph nodes: CLL (chronic lymphocytic leukemia) lymphosarcomatosis, lymph nodes tuberculosis, cancer metastases to lymph nodes and others. Clinical – hematologic patterns, lymph node cytologic and histologic examinations, results of bone marrow aspirates and iliac bone trepan biopsy examinations are the cases when differential diagnosis is necessary.

Treatment

There are two main methods of treatment: polichemotherapy and radiation therapy. As a rule combined treatment is used. It includes combined polichemotherapy and radiation therapy and takes into account stage of disease and process malignancy degree, which are determined by histologic variant.

Patients having lymphogranulomatosis are treated according to the following program: 3-4 courses of induction polichemotherapy with subsequent stage by stage irradiation of all main groups of lymph nodes on both sides of diaphragm.

2-3 courses of consolidation polichemotherapy are recommended after radiation therapy.

Radiation therapy is a very effective method used in lymphogranulomatosis treatment, as lymphogranulomatosis nodes are very sensitive to X – rays, which suppress specific vegetation in affected organs with development of connective tissue and its transition to fibrosis. High accumulated doses of radiation are directed to affected and outwardly unaltered regional lymph nodes to destruct the tumor cells.

In the process of combined treatment it is necessary to watch blood index (not less than once a week), prescribe symptomatic means (desintoxication measures if hematransfusion is necessary, antihistaminic drugs, group B vitamins and others), in case of necessity – antibiotics, antimycotic and other symptomatic agents. Myelocytokins: granulocytes (neupogen, filgrastim) or granulocyte – macrophages (leukomax, molgramostim) factors are recommended for prevention and treatment of neutropenia.

In case of relapse, therapy is renewed: local irradiation if single lymph nodes are affected or polichemotherapy with following irradiation if some zones are affected and if there are symptoms of intoxication.

Prognosis

60 – 80% of malignant lymphoma patients are completely curable in case of adequate treatment at early stage of disease. Cured patients can continue their working activity.

II. Non - Hodgkin's malignant lymphomas (NML)

Etiology and pathogenesis

Particularly characteristic of the lymphoid neoplasms is involvement of the antigen receptor genes in the molecular abnormalities. An increasing number of chromosomal translocations in lymphoid malignancy have been shown to involve deregulation of "master" genes involved in the regulation of other genes. In addition to changes in cellular genes, the expression of adventitious genes provided by viruses may contribute to the ultimate functional changes that give rise to neoplasia. The process is spread by metastasizing.

Classification

Nowadays Kilsch classification (1978), which is usually called NML of clinical use (1981) and modified Europe – American lymphoma classification (REAL – classification 1994) are widely used to detach separate forms of non – Hodgkin's malignant lymphomas. NML are subdivided into B and T – cell origin NML depending on the stage of their malignancy and substrate cells origin.

According to REAL classification B – cell origin NML are:

- 1) lymphoma from small lymphocyte / B – cell origin chronic lymphocytic leukemia (CLL)
- 2) immunocytome / lymphoplasmocytic lymphoma;
- 3) mantle zone lymphoma;
- 4) lymphoma from follicle centers, follicular lymphoma;
- 5) Marginal zone B – cell lymphoma;
- 6) Plasmocytoma;
- 7) Diffuse lymphoma from large B – cells;
- 8) Burkitt's lymphoma.

T – cell NML are:

- 1) peripheral T – cell lymphomas, non – elaborated lymphomas;
- 2) angioimmunoblast T – cell lymphoma;
- 3) angiocentric lymphoma;
- 4) T – cell intestinal lymphoma;
- 5) anaplastic large – cell lymphoma.

Non – Hodgkin's malignant lymphoma classification suggested by international group on lymphoma study (1998)

Inactive (low – grade malignancy lymphomas)

| Neoplasms of B – cell origin | Neoplasms T - cell origin |
|---|---|
| B – cell CLL / lymphoma from small lymphocytes; Lymphoplasmocyte lymphoma; Lymphoma from follicle centers, follicular lymphoma from small cells and mixed small and large cells; Marginal zone B – cell lymphoma; Hairy – cell leukemia; Plasmocytoma / plasm- cell myeloma. | Leukemia from big granulocontaining lymphocytes; T – cell leukemia / adult's lymphoma; Mycosis fungoides / Sezary syndrome. |

Moderate aggressive (middle grade of malignancy)

| B – cell origin | T – cell origin |
|---|---|
| B cell – prolymphocyte leukemia; Lymphoma from mantle – zone cells; Lymphoma from follicle centers, follicular lymphoma, from large cells | T – cell CLL (prolymphocyte leukemia) T – cell leukemia / adult's (chronical) lymphoma; Angiocentric lymphoma; Angioimmunoblast lymphoma |

Aggressive (high grade of malignancy)

| B – cell | T - cell |
|------------------------------|---|
| Lymphoma from B – cell group | Peripheral T – cell lymphomas; T – cell intestinal lymphoma; Anaplastic large cell lymphoma |

High aggressive (very high grade of malignancy)

| B - cell | T - cell |
|---|---|
| Lymphoblast leukemia / lymphoma from precursor B – cells; Burkitt's lymphoma; High degree of malignancy B – cell lymphoma – Burkett like. | Lymphoblast leukemia / lymphoma from precursor T – cells; T – cell leukemia / lymphoma (acute and lymphomatoid). |

Clinical classification of malignant lymphomas taking into account spread of pathological process, is general for lymphogranulomatosis and non – Hodgkin's lymphoma. There is one more stage for NML in which bone marrow leukemic lesion with lymphoma "leukimization" is observed. Two forms: A and B are distinguished in each stage. These forms depend on presence or absence of intoxication symptoms.

Clinical presentation

NML is characterized by enlargement of lymph nodes which are indurated and fused with each other in the form of huge packs at early stages. Clinical symptom in general depend on focus localization and function disorder of different organs. For instance squeezing symptoms of upper cava, dispnea, cyanosis, face and neck edema arise in mediastinum; mesenteric or retroperitoneal lymph nodes enlargement

can result in ascites and intestinal obstruction; obstructive jaundice arises in hepatic duct at squeezing of general bile duct by lymph nodes; reticular symptoms and even paraplegia in the result of tumor penetration into vertebra and spinal cord squeezing arise at localization of affected lymph nodes near spinal cord.

Apart from lymph nodes, different organs and tissues (such as: liver, spleen, tonsils, nasal part of pharynx, stomach, intestine, pleura, lungs, bones, skin soft tissues, bone marrow and so on) are often involved in this process. Fever, and cachexia are common for this disease. Blood changes don't have specific particularities: red blood usually doesn't change, number of leukocytes can be normal, decreased or can be moderate neutrophil leukocytosis, ESR is usually above normal rate.

Bone marrow lesion (leukemisation) is revealed more often at prolymphocytic lymphosarcoma and develops as prolymphocytic leukemia or CLL with corresponding clinical symptoms. Leukemisation develops as ALL (acute lymphoblast lymphoma) at lymphoblast lymphosarcoma. Mediastinal is affected at this form of lymphoma. Early generalization of the process is characteristic for lymphocytic variant.

Diagnosis

Diagnosis verification is based on open biopsy of lymph node with following microscopic examination and immunohistochemical study.

Treatment

The treatment is the same as Hodgkin's lymphoma therapy. It includes radiation and polychemotherapy. The treatment takes into account the stage of malignancy process and the stage of disease.

Prognosis

Prognosis depends on process stage and to some degree from cytomorphological variant. Nodular NML forms have more favorable prognosis than, generalized forms. The best prognosis is for patients with lymphomas having low and intermediate grade of malignancy. Therapy intensification gives good results, so patients with NML and lymphogranulomatosis nowadays have more favorable prognosis than it was before. The patients can be cured.

Questions for self control

1. Etiology of lymphoproliferative diseases development.
2. Hodgkin's lymphoma classification.
3. The example of Hodgkin's and non Hodgkin's lymphoma diagnosis formulation.
4. Methods of diagnosis verification
5. Lymphoproliferation diseases treatment.

Tests (choose the correct option)

1. Hodgkin disease is:

- a) skin cancer;
- b) sarcoma;
- c) hematology;
- d) oncohematology;
- e) metastases from malignant tumors.

2. The second stage of Hodgkin's disease.

- a) lesion of the first group of lymph nodes;
- b) lesion of lymph node groups on both sides of diaphragm;
- c) lesion of two or more groups on one side of diaphragm;
- d) lesion of extra nasal zones.

3. For diagnosis verification it is necessary:

- a) CT of three zones;
- b) lymph nodes open biopsy;
- c) clinical blood test, biochemical blood test, coagulation blood test;
- d) thoracoscopy, laparoscopy.

4. Risk factors.

- a) insolation;
- b) Epstein – Barr virus;
- c) heredity;
- d) chemical substances;
- e) radioactive radiation;
- f) everything mentioned above;

5.Hodgkin's lymphoma treatment.

- a) surgical;
- b) polychemotherapy;
- c) radiation therapy;
- d) radioiodine treatment;
- e) chemoradiation therapy.

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

SOFT TISSUE AND BONE TUMORS

Soft tissue tumors

Soft tissue sarcomas refer to malignant tumors arising in the soft tissues and they are grouped together because of similarities in pathologic appearance, clinical presentation and behavior.

The soft somatic tissues are ubiquitous and comprise more than 50% of body weight. Because of the nature of connective tissue, soft tissue sarcomas can arise anywhere in the body.

Incidence

Sarcomas are rare tumors compared to other malignancies: 8.900 new sarcomas in 2012 year, with 4.400 deaths.

The incidence and mortality from soft tissue sarcomas (STS) have been increasing. STS comprise 0.7% of all cancers and 6.5% of all cancers in children younger than 20 years. STS rank fifth in cancer incidence among children younger than 15, behind leukemia, central nervous system cancers, lymphomas, and sympathetic nervous system cancers.

These neoplasms constitute only 0.2 – 2.6% of malignant tumors and affect equally often men and women, more common at the age of 20 – 50 years.

Soft tissue tumors

Soft tissue refer to extraskeletal connective tissues of the body that connect, support and surround other discrete anatomic structures. They are:

- muscles;
- tendons;
- ligament;
- skin;
- fat;
- bone;
- cartilage;
- nerves;
- blood vessels;

- lymphatic vessels.

Supportive tissue structures:

- fibrous tissue;
- synovial tissue.

Malignant tumors are categorized as sarcomas if they arise from connective tissue.

Cartilage tumors start in the bone, not in the joint.

Soft tissue sarcomas risk factors

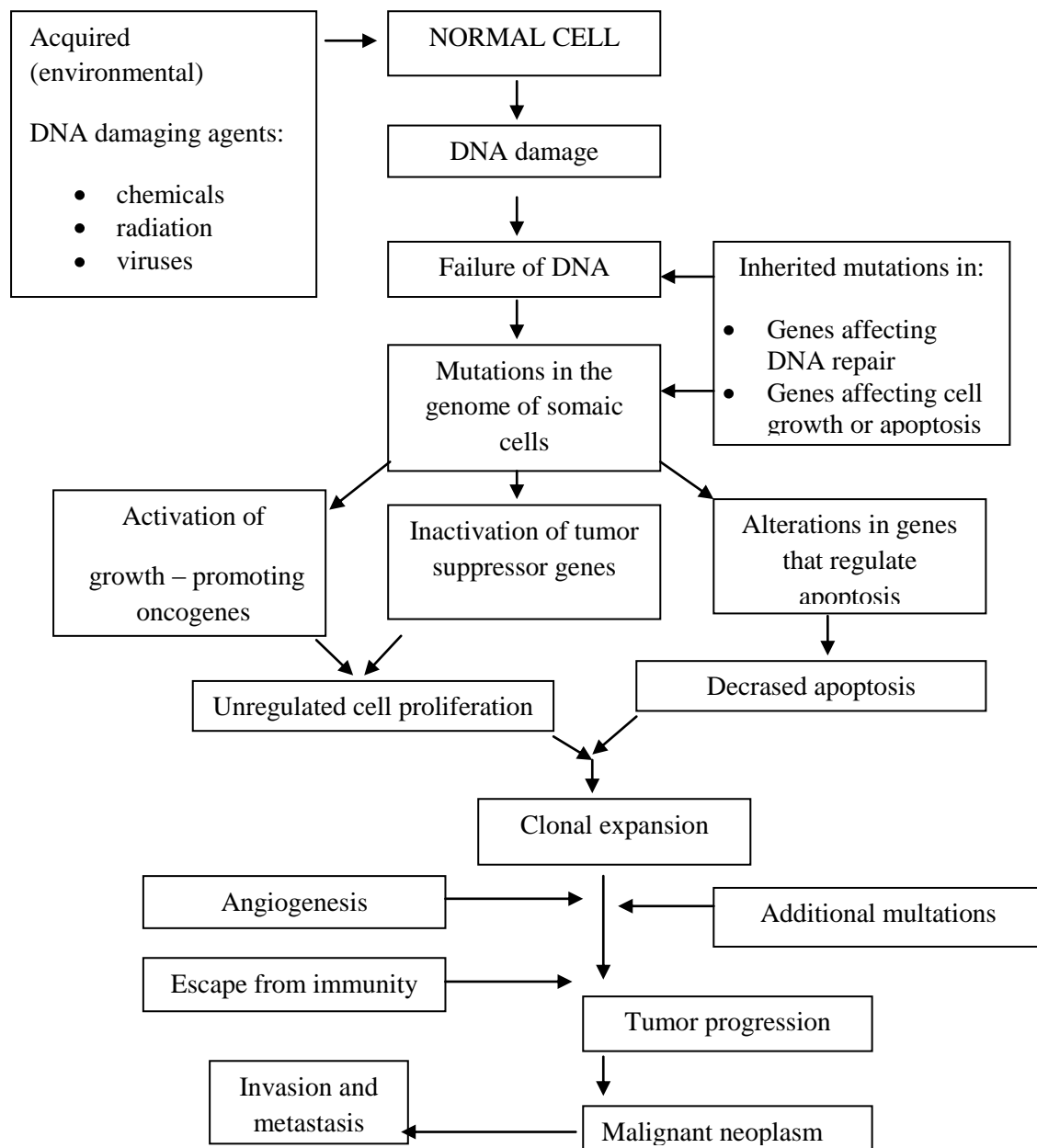
- Little is known about epidemiologic or etiologic factors.
- The known etiologic agents are
 - 1) Ionizing radiation (Sarcomas have a tendency to occur in areas previously exposed to ionizing radiation).
 - Radiation latent period sarcomas develop in 1% of patients who have undergone therapeutic irradiation.
 - The interval between irradiation and diagnosis of sarcoma varies between 5 and 10 years.
 - The majority of radiation-induced sarcomas are high grade and poorly differentiated.
 - 2) Oncogenic viruses:
 - Oncogenic viruses introduce new genomic material in the cell, which encode for oncogenic proteins that disrupt the regulation of cellular proliferation.
 - Two DNA viruses have been linked to soft tissue sarcomas:
 - *Human herpes virus 8 (HHV8) linked to Kaposi's sarcoma*
 - *Epstein-Barr virus (EBV) linked to subtypes of leiomyosarcoma*
 - In both instances the connection between viral infection and sarcoma is more common in immunosuppressed hosts.
 - 3) Chemical carcinogens:
 - Exposure of Vietnam veterans to "Agent Orange" a mixture of two commercial phenoxyacetic acid herbicides.
 - Herbicides ("agent orange") and peripheral soft tissue sarcomas.
 - Retained metal objects (shrapnel, surgical devices) and AS and MFH.
 - Vinyl chloride, inorganic arsenic, Thorotrast, anabolic steroids linked to AS and MFH.
 - These agents are able to cause genetic alterations that can lead to tumorigenesis.

- Host factors may also play a role in the development of soft tissue sarcomas.
 - Immunosuppression, besides Kaposi’s sarcoma, may be associated with sarcomas.
 - Lymphedema, congenital or acquired (post-mastectomy) is a rare cause of extremity-based AS. (Fig. 34).
- 4)Injuries.
 - 5)Chronic inflammatory process.
 - 6)Benign tumors.



Fig. 34 Lymphedema

Each of soft tissues can give rise to benign and malignant tumors.



Classification

Purpose of classification is to link similar tumors in order to understand their behavior, determine the most appropriate treatment, and investigate their biology. Soft tissues are classified according to the cell type they resemble.

- All tumors are derived from stem cells that are programmed to differentiate into various mature cell types.

- Some of the stem cells probably belong to local, organ-specific pools, as underscored by the fact that many tumors resemble tissues present in the region
- Other involved stem cells may be bone marrow derived.
- However, some tumors have no resemblance to normal tissue in the region (metaplastic foci within a tumor, or tumors of different histogenesis from the normal cells of the region)
- Some sarcomas have no normal cell counterparts, probably reflecting a unique genetic makeup.
- Refinements are coming from cytogenetics, molecular, and gene expression studies.
- The majority arise from -or show differentiation toward-mesenchymal cells,
- but some show other differentiation (neuroectodermal, histiocytic).
- A small subset is of unknown histogenesis.
- Tumors are also classified according their biologic potential.
- A three-tiered system is used:
 1. **Benign**
 2. **Borderline (intermediate malignant)**
 3. **Malignant.**

| MAJOR TYPES OF SOFT TISSUE TUMORS | | |
|--|-----------------------------|--------------------------|
| Cell type | Benign tumor | Malignant tumor |
| Fibroblast | Fibroma, myxoma | Fibrosarcoma, MFH |
| Adipocyte | Lipoma | Liposarcoma |
| Smooth muscle cell | Leiomyoma | Leiomyosarcoma |
| Skeletal muscle cell | Rhabdomyoma | Rhabdomyosarcoma |
| Endothelial cell | Hemangioma | Angiosarcoma |
| Schwann cell | Schwannoma, neurofibroma | MPNST |
| Cartilage cell | Chondroma | Chondrosarcoma |
| Interstitial cell | GIST | GIST |
| Histiocyte | JXG, GCTTS, RDD | True histiocytic sarcoma |
| Unknown | No benign counterparts | ES, SS, ES, ASPS |

Immunohistochemistry

- Immunohistochemistry evaluates the presence of certain protein and carbohydrate epitopes on tissue sections.
- Evaluation of cell- or tumor-type specific or cellcycle related markers may have diagnostic significance.
- Very few markers are specific for one tumor type.
- No cell-cycle marker is able to separate benign and malignant tumors.
- Myofibroblastic tumors: SMA, HHF35
- Smooth muscle tumors: desmin, SMA, HHF35
- Skeletal muscle tumors: desmin, myogenin, Myo-D1, myoglobin
- Nerve sheath tumors: S-100 protein, CD34, EMA
- Fatty tumors: S-100 protein
- Synovial sarcoma: CK, EMA, S-100
- Epithelioid sarcoma: CK, CD34
- Carcinomas: CK, EMA
- Melanoma: S-100, HMB45, tyrosinase, Melan A

Staging

- The stage is an estimate of the extent or dissemination of a tumor (and in the current systems includes tumor grade). Grades are assigned from grade 1 (well – differentiated) to grade 3 (poorly differentiated).
- Staging is important for planning of treatment and prognostication.
- Clinical data and imaging studies are part of staging process.
- Visceral sarcomas excluded.

Classification of Soft tissue tumors by TNM system

Primary tumor (T)

T1 < 5 cm

T1a – Superficial to muscular fascia

T1b – Deep to muscular fascia

T2 – 5 cm

T2a – Superficial to muscular fascia

T2b – Deep to muscular fascia

Regional lymph nodes (N)

N0 – No regional nodal involvement

N1 – Regional nodal involvement

Distant Metastasis (M)

M0 – No distant metastasis

M1 – Distant metastasis

Grouping of Soft Tissue Sarcomas in stages

Stage IA G1,2 T1a,b N0 M0

Stage IB G1,2 T2a N0 M0

Stage IIA G1,2 T2b N0 M0

Stage IIB G3,4 T1a,b N0 M0

Stage IIC G3,4T2a N0 M0

Stage III G3,4T2b N0 M0

Stage IV Any G, Any TN1M0, Any G Any T Any N M1

"a" superficial tumors of trunk and extremities (above fascia)

"b" deep tumors of trunk and extremities or intra – abdominal, intra – thoracic or retro – peritoneal.

Soft tissue tumors metastases

- For each histologically distinct malignant sarcomas, the tendency to metastasize depends on the grade of the tumor.
- The route of metastases is usually hematogenous, and the lungs are the most frequent site of involvement (60 – 80%).
- Lymphatic metastasis occurs in less than 20% of cases and usually later than the hematogenous one.
- Almost half of the patients, with high – grade STSs develop metastatic disease, most frequently in lungs.

Clinical presentation

Symptoms generally result from pressure or traction on adjacent nerves or muscles. Symptoms are few until the lesions are quite large compared with the anatomic part. All soft tissue lumps that persist or grow should be biopsied.

These tumors are usually painless mass. There are poor symptoms at the early stage of disease.

The more common symptoms of soft tissue sarcomas are:

- presence of the tumor;
- pain;

- neurological symptoms when the tumor presses greater nerves or / and vessels.

It is important to differentiate locally aggressive, nonmetastasizing lesions from those that are truly benign or malignant because of the therapeutic implications. There are no reliable physical signs to differentiate benign from malignant soft tissue lesions.

Diagnosis

Soft tissue sarcomas most often present as asymptomatic soft tissue masses.

- history (anamnesis);
- clinical presentation;
- US (dopplerography);
- radiological examination;
- CT; } evaluate the tumor's relation to major neurovascular and
- MRI; } skeletal structures.
- angiography;
- osteoscintigraphy;
- biopsy: excisional biopsy is an appropriate means of establishing a diagnosis only for STS_s smaller than 3 cm in diameter; incisional biopsy is indicated for tumors larger than 3 cm in diameter; multiple core – needle biopsy can provide adequate pathologic material, aspiration cytology is typically not sufficient;
- immunohistochemistry;
- bone scan;
- lymphangiography is rarely undicated (STS infrequently metastasize to regional lymph nodes).

Treatment

Surgery

Surgery alone, surgery combined with radiation, surgery combined with radiation and endoarterial or intraarterial chemotherapy, or radiation alone have been used for the treatment of ST sarcomas.

Surgical resection is the main method of therapy for localized primary soft – tissue sarcoma. The majority of patients with localized soft – tissue sarcoma of the extremities undergo radical operations:

- limb sparing surgery (the tumor is removed with a margin of normal surrounding tissues, taking into account the fascial zones) the function of the extremity is preserved if the process does not involve major nerves and / or vessels.
- amputation of the digit (with endoprosthesis replacement of the joints, if it is possible). Sometimes cryotherapy can be used.

Nowadays less than 10% of patients undergo amputation.

- below – knee amputation is performed about a third the distance between the knee and the ankle.
- above knee amputation.

Radiotherapy

Radiotherapy alone in the management of STSs has been limited to the patients who have locally advanced, inoperable, recurrent, metastatic disease or if the patient refuses from the operation.

Adjuvant radiotherapy is realized in a classic regimen of the fractions with 30 – 60 Gy. Neoadjuvant radiotherapy is conducted by big fractions (5Gy) during 4-5 sessions.

Chemotherapy

Adjuvant chemotherapy can prevent metastatic spread. Endoarterial chemotherapy is more effective than the intraarterial one. Soft tissue tumors treatment begins with endoarterial chemotherapy during 4 days (1-4 courses with 21 – 28 days intervals depending on the treatment effect) with cisplatin, doxorubicin, metotrexat.

Prognosis

The poor prognosis of most patients with Soft Tissue Sarcomas is due to the tendency of these lesions to invade aggressively into surrounding tissue and for early hematogenous dissemination, usually to the lungs.

Factors thought to be of prognostic importance in patients with soft tissue sarcomas are: the histologic grade, site (proximal or distal; extremity or trunk), size, lymph node involvement.

5 year survival:
stage I } 70 – 80%
stage II }

stage III }
stage IV } > 30%
stage V }

Distant metastases (to the lungs, bones, liver and brain) are the more common cause of death.

Bone tumors

Bone sarcomas (Fig. 35, 36) are tumors of connective tissue. They are very rare (bone sarcomas: 1/10 of soft tissue sarcomas).

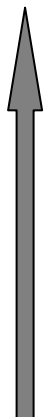
The malignant tumors arising from the skeletal system are rare. Osteosarcoma and Ewing's sarcoma are the two most common bone tumors, they occur mainly during childhood and adolescence. Other mesenchymal (spindle cell) neoplasms (fibrosarcoma, chondrosarcoma, and malignant fibrous histiocytoma) arise after skeletal maturity and they are less common.

Incidence

Osteosarcoma is the most common primary malignant tumor of bone (35%), followed by chondrosarcoma (25%) and Ewing sarcoma (16%). Chordomas and MFH represent 8 and 5% of the tumors in the group respectively.

The peak incidence of osteosarcoma is in patients between 10 to 19 years of age, or between 40 and 60 years (chondrosarcoma).

The carcinomas most frequently involved with bone metastasis originate from:

- 
- **Lung**
 - **Breast**
 - **Prostate**
 - **Kidney**
 - **Thyroid**

Tumor of adulthood (majority of patients > 50 years):

- chondrosarcoma (malignant neoplasm with pure hyaline cartilage differentiation);
- reticulosarcoma;
- fibrosarcoma.

Bone tumors risk factors

The majority of bone sarcomas arise de novo. They are very rare that's why not much is known about the etiology and risk factors of bone tumors.

High risk:

- Ollier and maffucci syndrome; familial Retinoblastoma syndrome.
- Rothmund – Thompson syndrome.
- Exposure to chemicals:
 - Vinyl chloride, used in plastics production.
 - Dioxin, an unwanted byproduct of incineration.
 - Herbicides containing chemical phenoxyacetic acid.
- Metallic and polyethylene implants.

Bone tumors metastases

Bone tumors unlike carcinomas, disseminate almost exclusively through the blood; bones lack a lymphatic system. Hematogenous spread

is manifested by pulmonary involvement in its early stages and secondarily by bone involvement. Bone metastasis is occasionally the first sign of dissemination.

The majority of tumors involving bone are secondary (or metastatic):

- secondary (metastases) (95%)
- primary (5%)

Bone – forming tumors

Osteoid osteoma

- Benign bone forming tumor.
- Small size, limited growth potential and disproportionate pain.
- Most common in long bones, but every bone may be affected.
- It may be painful on physical examination
- It may be associated with redness of skin and swelling.
- Lesions close to a joint may be associated with joint effusion.

Osteosarcoma

- Osteosarcoma is a high – grade, most common malignant spindle cell tumor arising within a bone.
- Malignant primary neoplasm of bone that produces osteoid (osteoid directly produced by the tumor cells).
- Intra – medullary original (conventional type).
- Rare subtypes.
- Most common, non – hematopoietic tumor of bone (incidence 4-5 per million)
- A disease of all age groups.
- 30 % >40 years, 60% < 25 years.
- In older people rule out predisposing conditions (e.g. Paget's disease of bone, radiation)
- Long bones of appendicular skeleton are favored
- 91% metaphysis, 9% diaphysis

Ewing's sarcoma is the second most frequent tumor in the teenage group.

Lymphoma is less common than Ewing's sarcoma and occurs in an older age group.

Chondrosarcoma is rare in childhood but becomes more prevalent with an advancing age.

Parosteal osteosarcoma is a low – grade malignant tumor, occurs in the late teens to 40 – year age group.

Clinical presentation

- The clinical presentation of bone tumors is at the beginning non-specific, with pain and swelling presenting first.
- Later, limitation of movement and pathological fracture and general symptoms may occur.
- A long time may elapse until the tumor is diagnosed.

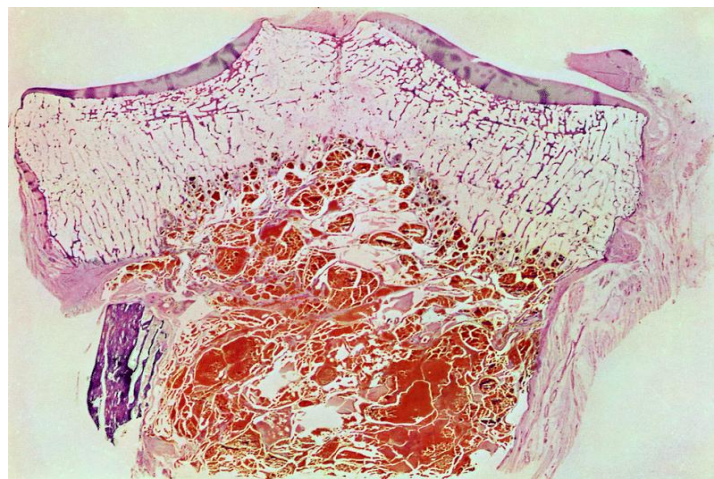


Fig. 35

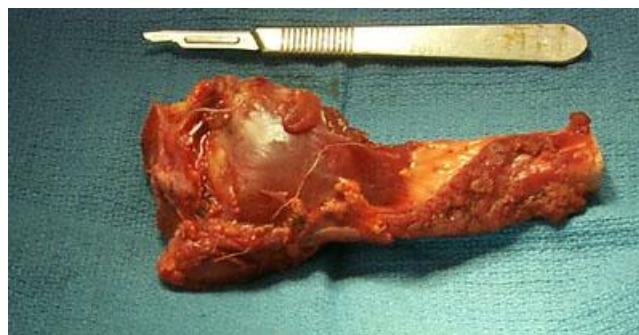


Fig. 36 Bony tumors and may be the most common bone tumor in the young adults

Diagnosis

Radiographic evaluation, combined with the clinical history and histology, is necessary for accurate diagnosis. The imaging characteristics of some lesions are diagnostic.

The diagnosis is based on:

- 1) anamnesis (history);
- 2) symptoms and signs;
- 3) radiological examination (Fig. 37, 38)
- 4) CT } are important in delineating the extent of local involvement;
- 5) MRI }
- 6) angiography;
- 7) bone scintigraphy (dynamic bone scans are based on tumor blood flow and regional plasma clearance by bone and soft tissue);
- 8) US (evaluates the extent of soft – tissue involvement, doplerography);
- 9) There are the following types of biopsy:
 - excisional biopsy (is indicated for lesions less than 3 cm. in diameter);
 - incisional biopsy;
 - needle biopsy;
 - fine needle aspiration;
 - trepan or core biopsy (preferred in limb – sparing) is an option, because it entails less local contamination than open biopsy. Core biopsy is helpful in difficult areas (spine, pelvis and hips);
 - trepan – biopsy is not descriptive;
- 10) conventional radiographs are still important in the diagnosis of bone tumors. A bone tumor is evaluated by five radiographic parameters: anatomic site, borders, bone destruction, matrix formation, and periosteal reaction. Bone destruction is the mark of a bone tumor. Bone destruction is described as a geographic, moth – eaten, or permeative pattern.

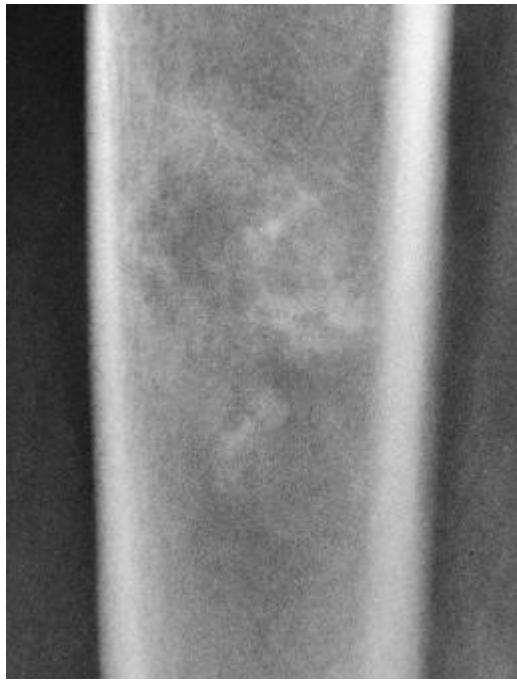


Fig. 37. .Geographic with sharp margins and flocculent calcifications (Enchondroma)



Fig. 38 . Sclerotic margin and lytic (Chondroblastoma)

Many tumors are site-specific and have a characteristic radiographic appearance (Fig 39.):

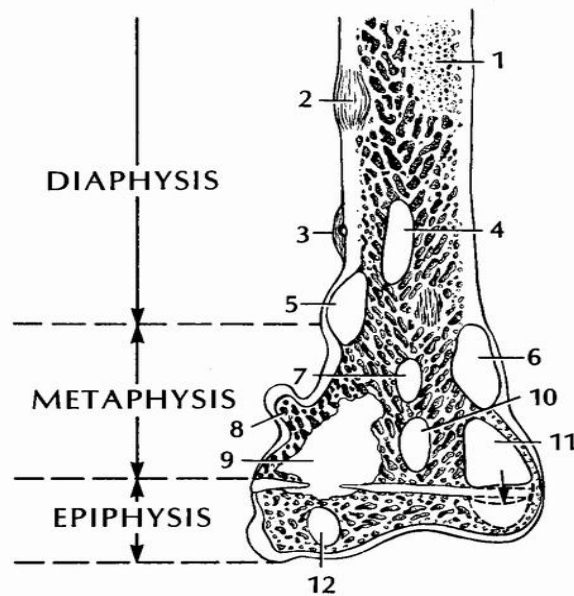


Fig. 39.

1. Ewing sarcoma, lymphoma, myeloma.
2. Osteofibrous dysplasia, adamantinoma.
3. Osteoid osteoma.
4. Fibrous dysplasia.
5. Chondromyxoid fibroma.
6. Non-ossifying fibroma.
7. Bone cyst, osteoblastoma.
8. Osteochondroma.
9. Osteosarcoma.
10. Enchondroma, chondrosarcoma.
11. Giant-cell tumor.
12. Chondroblastoma.

Classification and types of bone tumors

Bone consists of cartilaginous, osteoid, and fibrous tissue and of bone marrow elements. Each tissue can give rise to benign or malignant spindle cell tumors. Cell type and recognized product of proliferating cells are the base of bone tumors classification. Radiographic, histologic, and clinical data are used to diagnose and determine the degree of activity and malignancy of each lesion.

Patterns of spread and classification

Benign and latent tumors grow slowly during normal growth of the person and then stop. They never become malignant.

Benign and active tumors grow progressively.

Benign and aggressive tumors that are locally aggressive but do not metastasize. The tumor extends through the capsule into the reactive zone.

Low – grade malignant tumors have a low potential to metastasize. They have a pseudocapsule.

High – grade malignant tumors grow rapidly and metastasize early.

The tumor need to be graded (grading is an important element of the staging and determines if the tumor is stage I or II).

The TNM system follows a 2 tier grading system: low- and high-grade.

Classification of bone sarcomas by TNM system

Primary tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Tumor less or equal to 8 cm in the greatest dimension

T2 Tumor equal or more than 8 cm in greatest dimension

T3 Discontinuous tumors in the primary bone site

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

Discontinuous tumors

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis: M1a: lung, M1b: other sites

Grouping of bone sarcomas in stages

Stage IA T1 N0, NX M0 Low grade

Stage IB T2 N0, NX M0 Low grade

Stage IIA T1 N0, NX M0 High grade

Stage IIB T2 N0, NX M0 High grade

Stage III T3 N0, NX M0 Any grade
Stage IVA Any T N0, NX M1a Any grade
Stage IVB Any T N1 Any M Any grade
Any T Any N M1b Any grade

Stage I: low grade intra-compartmental (risk of metastasis <25%)

Stage II: high-grade extra-compartmental (risk of metastasis >25%)

Stage III: any grade, discontinuous tumor in the primary bone site

Stage IV: any grade, metastatic

Treatment

There are six primary factors whose specific criteria depend on the considerations of six major functional anatomic regions. The primary functions are motion, pain, stability or deformity, strength, emotional acceptance and function and complications.

Surgical removal includes: curettage, resection and amputation and is the traditional method of managing skeletal neoplasms.

Type of surgery:

1. Cripple operation:

- amputation or;
- exarticulation of the extremity.

2. Limb – sparing operation consists of the following phases:

- excochleation;
- resection of the affected bone.

3. Skeletal reconstruction:

- resection of the joint parts of the bones with the following substitution of the defect by plastic materials, bone transplants, polymers (hydroxilapatite);
- endoprosthesis replacement of big joints with modern prosthetic devices;
- cryotherapy can sometimes be used;
- destructive osteosynthesis;
- cryotherapy can sometimes be used.

Resection of a bone tumor implies that the tumor is removed in total with surrounding uninvolved bone. The amount of bone depends on the anatomic situation and limitations.

Small low – grade lesions in the metaphysis may be safely resected by removing only a portion of the bone.

High – grade tumors that arise in the metaphysis close by or adjacent to the subchondral bone usually require removal of the adjacent articular surface. Bone sarcoma is a radioresistant tumor, therefore radiotherapy is only applied as adjuvant to surgery.

Chemotherapy

Neoadjuvant chemotherapy may be administered directly into the arterial supply of the tumor to maximize drug delivery, to the tumor vasculature.

5-6 courses of system adjuvant chemotherapy are usually indicated:

- ifosfamid 3 mg/m^2 and vincristine 1.4 mg/m^2 during 1 day; mesna 660 mg/m^2 every 4 hours during 48 hours after the infusion of ifosfamid; cisplatin 100 mg/m^2 during 3 days;
- doxorubicin 25 mg/m^2 1 to 3 days, cisplatin 100 mg/m^2 (prolonged infusion) during 1 day. The course of treatment is to be repeated every 3 – 4 weeks.

Radiotherapy for bone tumors

Irradiation is often used for Ewing's sarcoma family of tumors (ESFT), myeloma, and lymphoma of bone, but not for other bone tumors. The benefits of irradiation are the treatment of a larger local area than surgery, no operative risk, and no need to replace the normal tissue removed at surgery.

Patients who refuse surgery, or have tumors in axial locations may require radiation therapy (the dose of 50 – 60 Gy) and system chemotherapy (6 courses) can be used.

Tumors of the axial skeleton and facial bones are treated by a combination of limited surgery and radiation therapy.

Radiation therapy is not used in the primary treatment of osteosarcoma.

Prognosis

Prognosis depends very much on metastases and histological grade of tumor.

- Untreated is fatal (aggressive local growth and rapid hematogenous systemic metastasis).
- When treated with surgery alone, survival is limited.
- Age, gender, location, size, stage and laboratory tests are traditional prognostic factors.
- The most reliable indicator of survival is the response to preoperative chemotherapy (good prognosis >90% tumor necrosis).
- In good responders survival in 80-90% of cases is not unusual.
- Bad responders, without change in chemotherapy, die in 80-90% of cases (but with change of regimen long-term survival can be greatly improved).

Questions for self control

1. Name connective tissue.
2. What are soft tissue sarcomas risk factors?
3. What is the route of soft tissue tumors metastases?
4. The symptoms of soft tissue sarcomas.
5. The methods of soft tissue sarcomas diagnoses.
6. What is the treatment of STS?
7. What are bone tumors risk factors?

Tests (choose the correct option)

1. Peak incidence of bone tumor

- a) 10 – 19 years and 40 – 60 years;
- b) the fourth decade of life;
- c) the third decade of life;
- d) the fifth decade of life.

2. What kind of biopsy is considered to be both diagnostic and therapeutic?

- a) true – cut biopsy;
- b) incisional biopsy;
- c) core needle biopsy;
- d) excisional biopsy.

3. Histologically, the most common primary malignant bone tumor of all age groups is

- a) osteoid osteoma;
- b) ewing's sarcoma;
- c) osteosarcoma;
- d) chondrosarcoma.

4. are less common bone tumors.

- a) secondary tumors;
- b) metastatic tumors;
- c) osteoblastic tumors;
- d) primary tumors.

5. Which is the most common therapy for localized primary soft – tissue sarcoma treatment?

- a) radiotherapy;
- b) chemotherapy;
- c) immunotherapy;
- d) surgery.

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

CANCER OF THE KIDNEY, URETER AND URINARY BLADDER

I. Kidney cancer

Incidence

Renal tumors (Fig. 40) account for about 3% of all neoplasms. In average 12.0 persons per 100.000 population had kidney cancer (KC) in 2012 year in Ukraine (in men 15.2, in women 9.3 cases). Men are twice as likely to develop this disease than women. Most cases of kidney cancer occur in persons aged 40 and older.

Risk factors

Cigarette smoking has been proved to be a definite risk factor. 30% of renal cell carcinomas in men and women are due directly to smoking. It is known that obesity is associated with an increased risk for development of kidney cancer. Many authors suppose that patients who abuse phenacetin – containing analgesics are also in an increased risk group for development of kidney cancer.

Renal cell carcinoma can develop at the end – stage of renal disease. Renal cell carcinoma is not a professional disease but occupational factors have been associated with the development of kidney cancer. There is an increased risk for development of kidney cancer among leather tanners, workers exposed to asbestos, cadmium and petroleum, shoe workers.

Pathology

There are 5 different cellular types of renal cell carcinoma:

- Clear cell (60 – 85%).
- Chromophilic (papillar) (7 – 14%).
- Chromophobic (4 – 10%).
- Oncocytoma (2-5%).
- Collecting ducts cancer (1 – 2%).

One of the main peculiarities of kidney cancer is that tumor thrombus can invade along intrarenal veins into the main trunk and then into inferior vena cava (ivc) sometimes up to the right atrium.

Clinical presentation

Kidney cancer presenting symptoms:

1) renal cell carcinoma symptoms present classic triad (hematuria, pain, palpable abdominal mass). 30% of the patients are asymptomatic, so renal symptoms are indicative of advanced disease, and occur in 8% of patients. Palpable abdominal mass in subcost as a rule is indicative of advanced disease. However it can be the first symptom of kidney cancer. But it is not always possible to diagnose kidney cancer because density and tuberosity of the tumor are difficult for palpation.

2) Extrarenal (systemic) symptoms of renal cell carcinoma:

- anorexia and cachexia (which may be not the result of intoxication);
- fever;
- hematologic dysfunction (including dysproteinemia) and neurologic dysfunction (neuromyopathy);
- fatigue;
- weight loss;
- pyrexia;
- hepatic dysfunction;
- endocrinopathy;
- dermatosis and joint lesion.

Some studies suggest that not large kidney cancer metastasizes very rarely.

However 5% of the patients have first manifestations of disease due to distant metastases in lung (cough, hemoptysis); in brain (sharp headache); in bones (recurrent or permanent radiculitis, intercostal neuralgia and etc.).

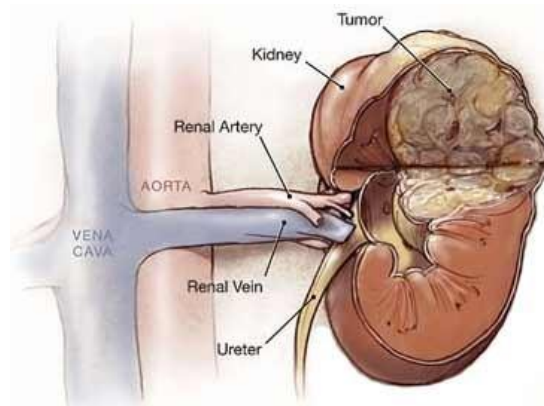


Fig. 40 . Kidney cancer

Classification of KC by TNM system

TNM stands for tumor, nodes, metastasis. TNM staging describes:

- the size of the primary tumor
- the number and location of any regional lymph nodes that have cancer cells in them whether the cancer has spread or metastasized to another part of the body

Primary tumor (T)

TX - Primary tumor cannot be assessed.

T0 - No evidence of primary kidney tumor.

T1 - Tumor is 7 cm or less and is confined to the kidney.

T1a – Tumor is 4 cm or less.

T1b – Tumor is larger than 4 cm, but not larger than 7 cm.

T2 - Tumor is larger than 7 cm, but is confined to the kidney.

T2a – Tumor is larger than 7 cm, but not larger than 10 cm, and confined to the kidney.

T2b – Tumor is larger than 10 cm, but is confined to the kidney.

T3 - Tumor has grown into the major vein of the kidney or the adrenal gland or into the tissues and fat surrounding the kidney, but not through Gerota's fascia.

T3a – Tumor has invaded the adrenal gland or the tissues and fat surrounding the kidney, but has not grown through Gerota's fascia.

T3b – Tumor has grown into the renal vein or into the vena cava (large vein in the abdomen leading to the heart) or to the wall of the vena cava below the diaphragm.

T3c – Tumor extends deeply into the vena cava or the wall of the vena cava above the diaphragm.

T4 Tumor has grown beyond Gerota's fascia, into neighboring structures.

Regional lymph nodes (N)

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.

Distant metastasis (M)

MX – Distant metastasis cannot be assessed.

M0 No distant metastasis.

M1 Distant metastasis.

Grouping of kidney cancer in stages

stage I T1 N0 M0 - Tumor is 7 cm or smaller and is limited to the kidney.

The cancer has not spread to the lymph nodes or other organs.

stage II T2 N0 M0 - Tumor is larger than 7 cm, but it is still limited to the kidney.

The cancer has not spread to the lymph nodes or other organs.

stage III T3 N0 M0 - Tumor has spread into the major vein of the kidney, the adrenal gland or to tissues and fat surrounding the kidney, but not through Gerota's fascia. Tumor may have grown into the vena cava. The cancer has not spread to the lymph nodes or other organs.

T1–3 N1 M0 - Tumor is any size. The cancer has spread to only 1 lymph node near the kidney.

stage IV T4 any N M0 - Tumor has grown through Gerota's fascia.

The cancer may have spread to only 1 lymph node, but not to any distant organs.

Any T N2 M0 - The cancer has spread to more than 1 lymph node near the kidney, but not to distant organs.

Any T any N M1 - The cancer has spread to distant organs, such as the lungs, bone, liver or brain.

Recurrent kidney cancer

Recurrent kidney cancer means that the cancer has come back after it has been treated. It may recur in the same location as the original cancer or it may recur in another part of the body (metastatic kidney cancer).

Diagnosis

Different diagnostic facilities are used to get information about renal tumors and evaluate them.

Laboratory studies.

They are as follows:

- Excretory urography.
- CT
- Ultrasound (cyst punch biopsy under US guidance). The combination of US and cyst puncture enables to make the correct diagnosis in most suspicious renal mass lesions.
- MRI – (magnetic resonance imaging).
- Arteriography.
- Venography.
- Transesophageal echocardiography (shows the extent of the vena cava involvement).

Additional studies:

- Echocardiography.
- Colonoscopy.
- Duodenography.
- Bone scan.

US, CT and MRI allow to diagnose space – occupying renal mass lesions in 95% of cases, define tumor localization (90%) and kidney cancer stage (80-85%). Ultrasound examination is used for screening tests. In case us scanning diagnoses an equivocal dense space occupying renal mass lesion. CT is recommended CT provides information about spreading of the process and the state of the regional lymph nodes. MRI provides good diagnostic information about vein tumor invasion. Sometimes punch biopsy under ultrasound quadrants should be performed.

All imaging facilities can be used to provide the complete information about renal tumor location, size, and extend of disease.

Treatment

Surgery

Surgical resection is the primary treatment for localized renal cell carcinoma. There are different surgical approaches to removal of kidney

cancer. The common approaches for radical nephrectomy are transabdominal and thoracoabdominal.

Standard operation is radical nephrectomy. The Kidney excised en block with surrounding perirenal fat, fascia and regional lymph nodes.

The patients with bilateral renal cell carcinoma or tumors in solitary kidneys undergo organ saving operations.

In some cases extracorporeal nephrectomy is followed by auto transplantation of kidney. Patients with hematuria, intoxication or sharp pain are recommended palliative nephrectomy. Radical combined operation is performed in patients with renal cell carcinoma invading neighboring organs (liver, colon, tail of the pancreas) without distant metastases.

Immunotherapy

Immunotherapy activates host immune mechanisms of patients. Interleukin – 2 (IL – 2) and interferon - α are used for treatment of the patients with metastatic renal cell carcinoma.

Patients with metastatic renal cell carcinoma (RCC) treated with IL – 2 had a 30% 3 – year survival. Patients treated with IL – 2 and interferon - α and also in combination with chemodrugs, for instance with fluorouracil – 5 have better results.

Radiation therapy

Kidney cancer is radiation resistant tumor. However patients with bone metastases benefit from radiation therapy used with palliative aim (to lessen pain and induce regression) and so have stable disease for long periods of time and prolonged survival.

Prognosis

Difference in survival of patients with renal tumor depends first of all on the stage of disease. Patient with renal vein involvement have the worst prognosis. The patients age is a very important prognostic factor. Patients under 40 have worse prognoses than the older ones. Some clinical symptoms of renal tumor (fever, varicocole) are also very bad prognostic factors. 5 – years survival: Stage I – 67%; Stage II – 59%; Stage III – 30%; Stage IV – 7%.

II. Ureteral cancer

Primary Upper Urinary tract tumor (UUTT) is an uncommon neoplasm that accounts for about 3% of all malignancies of the upper genitourinary tract. Most of UUT neoplasms develop in patients between ages 40 to 70.

Renal pelvis tumors constitute 7 to 10% of all kidney tumors. The incidence rate of primary pelvis tumor occurrences is 12.4 per 100.000 population in 2012 year in Ukraine (in men 20.1, in women 4.6 cases). Primary ureter neoplasms are met less rarely and constitute about 1% of all kidney cancers and upper urinary tract carcinomas (UUTC).

The probability of urinary bladder neoplasm occurrence is great in patients with upper urinary tract carcinoma.

Risk factors

- Smoking is the major cause of UUTC.
- Concrement in renal pelvis.
- Balkan endemic nephropathy increases the risk of ureter and pelvic neoplasm development (100 time multiplication).
- Patients with UUTC arterial hypertension.
- Hereditary factor.
- Exposure to chemical carcinogen.

Classification of UUTT by TNM system

T - Primary tumor

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Ta Non-invasive papillary carcinoma

Tis Carcinoma *in situ*

T1 Tumor invades subepithelial connective tissue

T2 Tumour invades muscle

T3 (Renal pelvis) Tumor invades beyond muscularis into peripelvic fat or renal parenchyma

(Ureter) Tumor invades beyond muscularis into periureteric fat

T4 Tumor invades adjacent organs or through the kidney into perinephric fat

N - Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single lymph node 2 cm or less in the greatest dimension

N2 Metastasis in a single lymph node more than 2 cm but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in the greatest dimension

N3 Metastasis in a lymph node more than 5 cm in the greatest dimension

M - Distant metastasis

M0 No distant metastasis

M1 Distant metastasis

Grouping of UUTT in stages

stage 0a T_a N₀ M₀

stage 0is T_{is} N₀ M₀

stage I T₁ N₀ M₀

stage II T₂ N₀ M₀

stage III T₃ N₀ M₀

stage IV T₄ N₀ M₀

Any T N₁₋₃ M₀

Any T Any N M₁

Clinical presentation

Hematuria is the most common symptom of renal pelvis and ureter. It is present in 70 to 95% of patients with these diseases. Colicky pain in lumbar region due to obstruction by clot or by tumor occurs in up to 40% of the patients.

Dysuria is present in 5-10% of the patients; general symptoms (weight loss, subfebrile temperature, hyporexia) are present in 5-15% of the patients. It is possible to palpate a flank mass in 10-20% of patients, which is indicative of advanced disease.

Diagnosis

- History (anamnesis).
- Palpation.
- Cytological examination of urine (atypical tumor cells).

- Excretory urography.
- Retrograde pyelography (delineates precise location of ureteral lesion).
- Cystoscopy.
- Ureteropyeloscopy.
- Abdominal CT.
- Ultrasonography.
- Chest X – ray.
- Bone scintigraphy.
- Brush biopsy.

Treatment

The main method of treatment is surgery. Chemo- and radiation therapies are adjuvant ones.

I. Nephroureterectomy is a common method of treatment, plus bladder resection, and in some cases, segment ureter resection. Patients with high – grade (G1) and moderate differentiated (G2) superficial (non – invasive) tumors of distal third of ureter undergo partial ureter resection.

After partial ureterectomy, urinary tract continuity is reestablished with ureteroneocystostomy.

- Patients with low grade and invasive tumors of distal third of the ureter undergo nephroureterectomy plus bladder resection.
- Ureteropyeloscopy.
- Electroresection.
- Electrocoagulation.
- Laser coagulation.
- Laparoscopy nephroureterectomy.
- Partial ureterectomy is preferable because it preserves the kidney.

II. Postoperative adjuvant therapy can be: systemic chemotherapy, radiation therapy, immunotherapy.

Chemotherapy is relatively effective for treatment of metastatic disease. The most common regiment is M – VAC (a four drug regimen consisting of methotrexate, vinblastin, doxorubicin, cisplatin).

Prognosis

Superficial ureter cancer is highly curable and has a good prognosis, with 5 – year survival rates of the patients. The 5 – year survival of the patients with ureter carcinoma is determined by the grade and stage of the disease.

Invasive tumors have poor prognoses (10-15%). Tumors deeply invasive in surrounding tissue and metastasizing distant organs are practically incurable.

III. Urinary bladder cancer

Incidence

Bladder cancer (BC) ranks the 8th in men and the 18th in women. The highest incidence is at the age of 60 and older. Men are twice as likely to develop bladder cancer than women. The incidence of bladder cancer is increasing annually. The incidence of urinary bladder cancer was 11.4 cases per 100000 population in 2012 year in Ukraine (in men 19.8, in women 4.3 cases).

Risk factors

- Exposure to toxic substances (increased risk for BC is observed in aniline dye workers).
- Cigarette smoking.
- Shistosomiasis.
- Chronic urinary tract infections.
- Leukoplakia.
- Tuberculosis.
- Chronic abuse of analgesic phenacetin and cyclophosphamide.
- Ionizing radiation.
- Diet (Intake of oil and margarine, potassium, vitamin C, β - carotene, may be reversely related to the development of bladder cancer).

Classification of UBC by TNM system

90% of bladder neoplasms are transition cell carcinoma (TCC), 10% are squamous cell carcinoma and adenocarcinoma.

T: Primary tumor

Tx: primary tumor can not be estimated.

T0: no evidence of primary tumor.

Ta: noninvasive papillary carcinoma.

Tis: preinvasive carcinoma: carcinoma in situ: "Flat superficial tumor".

T1: tumor that invades the subepithelial connective tissue or that invades the own lamina.

T2: tumor that invades the vesical muscular layer: It is divided as well in:

T2a: tumor that invades the superficial muscular layer or internal half.

T2b: tumor that invades deep the muscular layer or external half.

T3: tumor that invades beyond the muscular layer or that invades the perivesical grease. It is divided as well in:

T3a: microscopic invasion.

T3b: macroscopic invasion.

T4: tumor that invades structures adjacent to the urinary bladder. It is divided in two:

T4a: invasion of the prostate, uterus or vagina.

T4b: invasion of the pelvic wall or abdominal wall.

N: Regional lymph nodes

Nx: regional lymph nodes cannot be assessed.

N0: no regional lymph nodes.

N1: metastases in a single lymph node ≤ 2 cm.

N2: metastases in some lymph nodes 2-5cm or multiple metastases in lymph nodes not more than 5cm.

N3: metastases in lymph node > 5 cm.

M: Distant metastasis

Mx: distant metastasis can not be assessed.

M0: no distant metastasis.

M1: distant metastasis.

Grouping of UBC in stages

| | |
|-----------|-----------|
| stage 0a | Ta N0 M0 |
| stage 0is | Tis N0 N0 |
| stage I | T1 N0 M0 |
| stage II | T2a N0 M0 |
| | T2b N0 M0 |

| | |
|-----------|-------------|
| stage III | T3a-b N0 M0 |
| | T4a N0 M0 |
| stage IV | T4b N0 M0 |
| Any | T N1-3 M0 |
| Any | T Any N M1 |

Clinical presentation

- Hematuria (75% of patients with BC)
- Dysuria (indicates carcinoma in situ)
- Pain above pubis, perineum, sacrum.
- Flank pain (ureteral obstruction).
- Rectal pain (rectal obstruction resulting in constipation).
- Lower extremity edema (secondary to lymphatic or venous obstruction).

Diagnosis

- Cystoscopy and biopsy.
- Urine cytology (may detect low grade tumors or carcinoma in situ).
- Laboratory tests (bladder tumor antigen (BTA), BTA TRAK test, nuclear matrix protein (NMP – 22)).
- Intravenous urographe.
- CT – scan of the abdomen and pelvis enable visualization of the entire urothelial surface.
- MRI (magnetic resonance imaging).
- Chest X – ray (evaluates the bladder wall thickening but it provides no information about lymph node status and is less informative than CT or MRI).
- Radioisotope bone scan.
- Ultrasonography.

Treatment

The term superficial bladder cancer includes lesions of stage T0, Ta, T1 and Tis, a broad range of tumors from ones that can be considered benign lesions (e.g. papilloma T0 grade I) to life threatening (grade 3 T1 or Tis).

There are superficial (Tis – Ta – T1) and invasive (T2 – T4) bladder tumors.

Superficial BC treatment.

Transurethral resection (TUR) is the primary modality of treatment of superficial bladder tumors. All tumors must be removed and only smooth bladder muscle should be visible at the completion of the resection.

Patients after TUR of bladder cancer should be considered for intravesical therapy to minimize the rate of recurrence.

Intravesical therapy and Bacillus Calmette – Guerin (BCG) are used to treat patients with moderate to high risk of metastases. The most common agent for intravesical chemotherapy is mitomycin C. Thiotepa and doxorubicin are used as prophylactic agents and prevent disease progression.

Carcinoma in situ treatment

The basic treatment of UBC in situ is a 6 – week course of BCG. BCG significantly reduces tumor recurrence and the progression rate in high – risk patients. 70% of the patients have been alive 10 years after therapy.

T1G3 bladder cancer treatment

T1G3 BC has high tendency to progression, so cystectomy is recommended to these patients. Chemotherapy or BCG follows cystectomy and 50% of patients achieve a complete response to treatment.

Treatment of invasive UBC

Radical cystectomy – is the most common treatment used for muscle invading bladder en block with the prostate and seminal vesicles in men, and uterus, bladder, urethra, ovaries in women.

There are 3 alternative methods of urinary bladder substitutes:

- 1) ileal conduit (Bricker's operation);
- 2) urine collecting device;
- 3) urine removal into artificial bladder or into continent intestine.

Possibility to control urine derivation is the main factor defining the quality of life.

Patients after TUR of superficial bladder lesion can be safely followed with careful endoscopic surveillance. Endoscopic management may be indicated in inoperable patients to stop bleeding. Postoperative adjuvant chemotherapy is recommended after TUR of invasive bladder cancer.

Bladder resection (BR) is recommended very rarely only to the patients with solitary primary invasive tumor.

Recurrence rates 56 to 65.5% after bladder resection have been recorded. New tumors may occur at great distance from the site, which has been operated.

That's why cystectomy is preferable to bladder resection.

Radical radiation therapy is an alternative method of invasive BC treatment. It is not as effective as surgery. That's why radiation therapy is recommended to the patients not appropriate for surgical treatment or if surgery is refused.

Disseminated BC treatment

Lately BC patients with distant metastases have been treated with polychemotherapy (M – VAC – methotrexate, vinblastin, adriamycin). Nowadays gemcitabin and taxanes are used. They have proved to be as effective as MVAC but they are less toxic.

Prognosis

Prognosis depends on the stage and treatment. 50% 5 – year survival rate is recorded after radical cystectomy. Combined treatment (radiation therapy follows bladder resection) gives the best results. The 5 – year survival for patients with stages T1-2 is 50 is 80%, stages T3-4 is 20 – 30%.

Questions for self control

- 1) Risk factors of kidney cancer
- 2) Kidney cancer classification according to stages.
- 3) Kidney cancer clinical presentation.
- 4) Kidney cancer diagnoses.
- 5) Kidney cancer treatment.

- 6) Risk factors of ureteral cancer.
- 7) What are the symptoms of ureteral cancer?
- 8) What are the early methods of diagnoses?
- 9) Bladder cancer clinical presentation.
- 10) Bladder cancer diagnoses.

Tests (choose the correct option)

1. Kidney cancer occurs more frequently in

- a) uranium miners;
- b) heavy drinkers;
- c) non – smokers;
- d) persons who abuse phenacetin – containing analgesics.

2. Renal cell carcinoma symptoms present classic triad: hematuria, pain, palpable abdominal mass.

- a) true;
- b) false;
- c) may be;
- d) none of the above.

3. What is the primary treatment for localized renal cell carcinoma

- a) immunotherapy;
- b) chemotherapy;
- c) radiation therapy;
- d) surgery.

4. The major cause of upper urinary tract carcinomas is

- a) smoking;
- b) hereditary factor;
- c) exposure to chemical carcinogens;
- d) obesity.

5. The highest incidence in patients with urinary bladder cancer is:

- a) The 4th decade;
- b) The 5th decade;
- c) 60 and older;
- d) 10 to 18 years.

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

GYNECOLOGIC TUMORS

(Uterine cancer, cervical cancer, ovarian cancer)

I. Uterine cancer

Incidence

- Uterine cancer (UC) ranks the 1st in gynecologic cancers.
- The incidence of uterine cancer was 24.28 per 100.000 population in women in 2012 year in Ukraine.
- The medial age for patients with UC is 55 to 65 years.

Risk factors

- Early menses and late menopause.
- Long – term anovulation.
- Women, who have never been pregnant.
- Age over 40.
- Women, who do not experience regular cycle.
- Endometrium atrophy.
- Endometrium hyperplasia.
- Obesity.
- Type 2 diabetes.
- Breast cancer.
- Sclerocystic ovaries syndrome.
- Estrogen secreting tumors of the ovary.
- Estrogen given without progesterone in postmenopause.
- Tamoxifen intake.
- Hypertension.
- Lynch II syndrome.

Histology

Histologic types of malignant endometrial cancer:

- Endometrioid adenocarcinoma.
- High – differentiated mucinous adenocarcinoma.
- Adenosquamous carcinoma (favourable prognosis).
- Secretory carcinoma.

Rare histologic types:

- Serous – papillary adenocarcinoma.
- Light – cells adenocarcinoma.
- Squamous adenocarcinoma.
- Non – differentiated mucinous adenocarcinoma.

The FIGO staging classification was changed from a clinical staging system to a surgical staging in 1988. Patients who are considered medically inoperable are staged by the old clinical staging system.

The 1988 FIGO system requires evaluation of operative findings, such as histologic grade, depth of myometrial invasion, peritoneal cytology, pelvic and paraaortic nodal status, and evaluation for extrauterine spread. It seems likely that surgical staging provides a better evaluation of prognosis and provides valuable information for planning postoperative adjunctive therapy.

FIGO Corpus (Uterine) cancer staging

Old staging

I The carcinoma is confined to the corpus

IA The length of the uterine cavity is 8 cm or less

IB The length of the uterine cavity is 8 cm or more

Stage I case should be subgrouped by histologic type of the adenocarcinoma as follows:

G1 – Highly differentiated carcinomas

G2 – Differentiated adenocarcinomas with partly solid areas.

G3 – Predominantly solid or entirely undifferentiated carcinomas.

II The carcinoma involves the corpus and the cervix.

III The carcinoma extends outside the corpus, but not outside the true pelvis (it may involve the vaginal wall or the parametrium but not the bladder or rectum)

IV The carcinoma involves the bladder or rectum or extends outside the pelvis.

FIGO morphological staging classification (1988) and TNM staging, the 7th edition (2010)

| Stage TNM | Stage FIGO | |
|------------------------|-------------------------|---|
| T1a N0 M0 | Stage IA | Tumor is limited to endometrium |
| T1b N0 M0 | Stage IB | Invasion to < ½ myometrium |
| T1c N0 M0 | Stage IC | Invasion to > ½ myometrium |
| T2a N0 M0 | Stage IIA | Endocervical glandular involvement only |
| T1b N0 M0 T3a N0 M0 | Stage IIB Stage IIIA | Cervical stromal invasion Tumor invades serosa and / or metastasizes into fallopian tubes and or ovaries / or positive peritoneal cytology |
| T3b N0 M0 | Stage IIIB | Vaginal metastases |
| Any T N1 M0 | Stage IIIC | Metastases to pelvic or lumbar lymph nodes |
| T4a Nany M0 | Stage IVA | Spread to the urinary bladder or rectum mucosa |
| Tany Nany M1 | Stage IVB | Distant metastases, including intraabdominal and / or inguinal lymph node |

Clinical presentation

The common symptoms of UC are:

- Bloody vaginal discharges 70-90% patients.
- Bleeding after menopause (varies from abnormal serosanguineous discharge to frank bleeding).
- Pelvic pain or pressure (is usually a symptom of advanced disease).
- Weight loss.
- Pyometria in a postmenstrual woman.
- Serosanguineous discharges.

Diagnosis

- History (anamnesis).
- The major method of diagnoses is aspiration biopsy of the endometrium (90 – 98%).

- Endometrial scraping (curettage).
- Hysteroscopy.

Palpation:

- Bimanual gynecology examination.
- Rectal examination.
- Ultrasonography.
- Cytological examination.
- Chest X – ray.
- CT.
- MRI.
- Rectoromanoscopy.

Treatment

Surgery

The primary method of uterine cancer treatment is surgery. Sometimes the disease can be managed by combination of surgery and radiation therapy.

More than 90% of the patients undergo surgical extirpation (removal of the uterus and annexum). Sometimes surgeons combine this operation with a selective retroperitoneal (pelvic and lumbar) lymphadenectomy. Selective lymphadenectomy is used for diagnosis.

Radiation therapy

Radiation alone is used for the inoperable patient or if surgery is refused. There is removed intracavitary radiation therapy and adjuvant radiation therapy.

Chemotherapy

Combination therapy using irradiation and chemotherapy may be able to improve survival in advanced disease. Paclitaxel and cisplatin are very effective and give good results.

Hormonotherapy

Medroxyprogesteron, megestrol and tamoxifen are used in hormonal therapy.

These drugs give no complications. A progesterone – like hormone drug stops estrogen production.

Prognosis

Stage at diagnosis is also related to survival.

The 2 year survival rate in patients with endometrial stromal sarcoma treated by radiation therapy and surgery was 57%, and for those treated by surgery alone it was 37%.

5 – year survival in patients with UC.

Stage IA – 90%.

Stage IB – 88%

Stage IC – 83%

Stage IIA – 77%

Stage IIB – 70%

Stage IIIA – 65%

Stage IIIB – 55%

Stage IIIC – 47%

Stage IV – 27%

II. Cervical cancer

Incidence

Cervical cancer is the 2nd most frequent of the female genital cancers.

It affects more than 470.000 women a year.

The highest incidence countries are Haiti, Nicaragua, Bolivia, Guinea.

This disease has decreased in recent decade in industrialized countries.

The highest incidence is observed in the women under 35 years.

The incidence was 20.9 cases per 100000 population in 2012 year in Ukraine.

Risk factors

- Early beginning of sexual intercourse.
- Large number of sexual partners.
- Women who became pregnant at a young age.
- Cervical cancer is common in prostitutes.
- It is common in the second wives of men, who have been previously married to women who developed cervical cancer.
- It is rare in Jewish and Moslem women.
- The disease is infrequent in the women with inactive sexual lives (eg.nuns).
- Human pappiloma virus (HPV) infection, plays an important role in the transformation process and is associated with the development of cervical neoplasia.
- HPV types 16 and 18 are common in cervical intraepithelial neoplasia and invasive cancer.
- HPV infection is observed in patients with displasia of the cervix.
- UPV infection is responsible for about 90% of cervix displasia.
- Smoking.
- HIV infection.
- Chlamydia and trichomonal infections.
- Diet.
- Oral contraceptives.
- Multiple pregnancies.
- Hereditary factors of cervical cancer.

Screening

Cervical cancer can be prevented by screening with cervical cytological analysis.

Histology

Most carcinomas of the cervix are squamous cell carcinoma (70 – 80%), adenocarcinoma (10 – 20%) and poorly differentiated carcinomas (10%). Rare types of cervical carcinoma are: adenoid cystic carcinoma, glassy cell carcinoma, adenoid cystic carcinoma and mucoepidermal carcinoma.

There are exophytic, endophytic and mixed lesions according to anatomic growth.

Patterns of spread

Metastases usually occur by means of the lymphatics, although blood born metastases also occur. Spread by hematogenous dissemination is relatively unusual in the early stages of cervical cancer, but the risk increases with more advanced stages.

Staging

Two staging systems are frequently used in cervical cancer: FIGO, in collaboration with the World Health Organization (WHO), and TNM system of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC).

Classification of Cervical cancer by TNM and FIGO systems.

| TNM | | FIGO |
|------------|-----|---|
| Tx | - | Primary tumor cannot be assessed |
| T0 | - | No evidence of primary tumor |
| Tis | 0 | Carcinoma in situ |
| T1 | Ia | Cervical carcinoma confined to uterus (extension to corpus should be disregarded) |
| T1a | IA | Preclinical invasive carcinoma diagnosed only by microscopy. |
| T1a1 | IA1 | Minimal stromal invasion 3 mm or less |
| T1a2 | IA2 | Measured stromal invasion more than 3 mm but not more than 5 mm in depth taken from the base of the epithelium with a horizontal spread 7 mm or less. |
| T1b | IB | The depth of invasion is mon than 5 mm. |
| T1b1 | IB1 | Clinically visible lesion 4 cm or less in greatest dimension. |
| T1b1 | IB2 | Clinically visible lesion more than 4 cm |
| T2 | II | Cervical carcinoma invades beyond uterus but not to pelvic wall or to the lower third of vagina |

| | | |
|-----|------|--|
| T2a | IIA | Tumor without parametrial invasion |
| T2b | IIB | Tumor with parametrial invasion |
| T3 | III | Tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney |
| T3a | IIIA | Tumor involves lower third of vagina; no extension to pelvic wall |
| T3b | IIB | Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney. |
| | IV | Cervical carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the bladder mucosa or rectal mucosa. (Bullous edema is not sufficient evidence to classify a tumor as T4) |
| T4 | IVA | Spread to adjacent organs (bladder, rectum, or both) |
| M1 | IVB | Distant metastasis |

Regional lymph nodes (N) AJCC staging only, include paracervical, parametrical, hypogastric (obturator), common internal and externaliliac, presacral and sacral.

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

Distant metastasis (M)

- MX: Presence of distant metastasis cannot be assessed.
- M0: No distant metastasis.
- M1: IVB Distant metastasis.

Grouping of Cervical cancer in stages

| | |
|------------|-----------|
| Stage 0 | Tis N0 M0 |
| Stage IA | Tis N0 M0 |
| Stage IB | T1b N0 M0 |
| Stage IIA | T2a N0 M0 |
| Stage IIB | T2b N0 M0 |
| Stage IIIA | T3a N0 M0 |
| Stage IIIB | T1 N1 M0 |

| | |
|-----------|----------------|
| | T2 N1 M0 |
| | T3a N1 M0 |
| | T3b any N M0 |
| Stage IVA | T4 any N M0 |
| Stage IVB | any T any N M0 |

Clinical presentation

- Dense watery discharge.
- Contact bleeding (postcoital spotting).
- Bleeding can occur intermenstrually.

Blood stained whites:

- Rectal bleeding.
- Rectal tenesmus.
- Hematuria.
- Urinary frequency.

Pain is a late symptom:

- Low back pain.
- Leg pain (the result from limbo sacral nerves compression).
- Bone fractures.
- Recto – vaginal and vesicle – vaginal fistula.

Diagnoses

- History (anamnesis).
- Physical examination.
- Palpation.
- Biopsy.
- Cytology analyses.
- Colposcopy.
- Endocervical curettage.
- Proctoscopy.
- Hysteroscopy.
- Histologic analyses.
- Chest X – ray examination.
- Ultrasound.
- CT – scan.
- MRI.

- Bone scan.
- Rectoromanoscopy.
- Urography.
- Laparoscopy.
- Cervical conization (is the removal of a cone – shaped portion of tissue from the cervix).

Treatment

The therapeutic approach for cervical cancer is determined by stage, histologic type and grade, depth of invasion and the medical status of the patients. Patient's age at the diagnosis of CC is a prognostic factor. The common methods of CC treatment are surgery, radiation therapy or their combination.

Cervical conization of the cervix can be diagnostic or therapeutic. Cervical conization is the removal of a cone – shaped portion of the tissue from the cervix. Patients with severe dysplasia, intraepithelial lesion (CIN III) and microinvasive cervical cancer, women in whom the depth of invasion cannot be determined by biopsy are indicated cervical conization. This procedure is carried out in patients in whom there is a suspicion of involvement based on the smear and other analyses.

Modified extended extirpation (hysterectomy) of uterus and adnexa is indication in cases of less than 3 mm invasion if there is lymphovascular invasion. Stage IA2 carcinoma of the cervix can also be managed by this surgery.

Extended extirpation of uterus and adnexa (or only uterus without adnexa) so called Wertheim operation can be managed in combination with radiation therapy (pre – or post radiation) for stages IB – IIA invasive cervical cancer treatment.

Patients with stages IB2 – IIA of cervical cancer, stage IB1 with echographic evidence of metastases in pelvic lymph nodes and stage IIB with not large cervical infiltration are delivered preoperative irradiation.

Postoperative irradiation is delivered to the patients, who have contraindications to preoperative irradiation (pregnancy, inflammatory process or volumous neoplasia in uterus adnex), the patients with metastatic pelvic lymph nodes or positive surgical margins, which were found after hysterectomy (extirpation).

Stages IIB and III of cervical cancer are managed by radiation therapy: external gamma radiation of pelvic and intracavitary insertion.

Irradiation can be effective for palliation of pelvic pain or bleeding. Irradiation, chemotherapy and symptomatic therapy can be useful for patients with advanced tumors.

Patients who have low chance of cure with surgery and radiation treatment are candidates for chemotherapy (stage III or IV).

Two – agent regimens are often used and have activity against cervical cancer: cisplatin + 5 – fluorouracil, cisplatin + 5 – fluorouracil. Patients are treated with cisplatin based combinations. Toxicity of the combination regimens is substantial.

Prognoses

Survival of the patients after surgical treatment depends on: lymph node metastases, tumor size, depth of invasion and tumor parametrial infiltration. The 5 - year survival rate of surgery alone or combined with preoperative or postoperative radiation therapy varied from 70 to 92%.

III. Ovarian cancer

Incidence

- 165.000 new patients with ovarian cancer (OC) are diagnosed yearly in the world and more than 100.000 women die from this disease.
- The incidence was 22.5 cases per 100.000 population in 2012 year in Ukraine.

Risk factors

- Disordered endocrine function.
- Most ovarian tumors arise in women after menopause in the age of 65 and older.
- Women with breast cancer have twice the expected risk for ovarian carcinoma.
- Exposure to asbestos and talc.
- Hereditary ovarian cancer.
- Older ages of the first pregnancy.
- Women who haven't been pregnant.

Histology

International Federation of Gynecology and Obstetrics (FIGO) adopted the classification of Malignant Ovarian tumors.

- Surface epithelial – stromal tumors are the most common and prototypic ovarian cancers. They include:
 - serous cystadenocarcinoma.
 - mucinous cystadenocarcinoma.
- Sex cord – stromal tumors include lesions that are hormonally active:
 - estrogen – producing granulosa cell tumor ;
 - virilizing Sertoli – Leyding cell tumor or arrhenoblastoma.
- Germ cell tumors originate from dysplastic germ material and tend to occur in young women and girls. Lesions include:
 - dysgerminoma, a form of choriocarcinoma;
 - malignant forms of teratoma.

Clinical FIGO and TNM, 7th edition (2010) classifications

| FIGO | TNM | |
|------------|---------|---|
| Stage I | | Growth limited to the ovaries |
| Ia | T1aN0M0 | Growth limited to one ovary |
| Ib | T1bN0M0 | Growth limited to both ovaries |
| Ic | T1cN0M0 | Tumor with capsule ruptured, or with ascites present |
| Stage II | | Growth involving one or both ovaries with pelvic extension |
| Stage IIa | T2aN0M0 | Extention and / or metastases to the uterus and or tubes |
| Stage IIb | T2bN0M0 | Pelvic extension |
| Stage IIc | T2cN0M0 | Ascites present containing malignant cells or with positive peritoneal washings. |
| Stage III | | Tumor spreads outside the pelvis, but is limited to the true pelvis, may be malignant extensions to lymph nodes |
| Stage IIIa | T3aN0M0 | Microscopic seeding of abdominal peritoneal surfaces |
| Stage IIIb | T3bN0M0 | Macroscopic peritoneal metastases less than 2cm. |

| | | |
|------------|----------------------|--|
| Stage IIIc | T3cN0M0 | Macroscopic peritoneal metastases exceeding 2 cm in diameter, positive regional lymph nodes. |
| Stage IV | T1-3N1M0 T1-3N0M1 | Distant metastases and / or metastatic pleuritis. |

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

Mx – Presence of distant metastasis cannot be assessed

M0 – No distant metastasis

M1, IVB – Distant metastasis

Clinical presentation

Ovarian cancer is asymptomatic in early stage. Most patients are not diagnosed until the disease is advanced. The main presenting symptoms are: pain, abdominal distention, lower abdominal discomfort, nausea and vaginal bleeding appear at advanced diseases.

- sensation of pelvic heaviness;
- abnormal menstrual cycles;
- back pain that worsens over time;
- increased abdominal girth.

Nonspecific gastrointestinal symptoms:

- vague lower abdominal discomfort;
- increased gas (distention);
- indigestion;
- inability to ingest usual volumes of food;
- lack of appetite;
- nausea and vomiting;
- bloody stool;
- bloating.

Additional symptoms that may be associated with the disease:

- increased urinary frequency / urgency;
- fluid buildup in the lining around the lungs (pleural effusions);

- excessive hair growth;
- positive pregnancy readings in the absence of pregnancy (this is for germ cell tumors only).

Diagnosis

Diagnosis includes:

- careful history;
- symptoms;
- physical examination (may reveal increased abdominal girth and / or ascites (fluid within the abdominal cavity));
- breast examination;
- pelvic examination (may reveal an ovarian or abdominal mass. Pelvic examination can include a rectovaginal component for better palpation of the ovaries);
- instrumental examination;
- laboratory examination.

Instrumental examination:

1. Abdominal ultrasound.
2. Ultrasound of the small pelvis.
3. Trans – vaginal ultrasound.
4. CT scan of the abdomen and pelvis.
5. MRI.
6. Cystoscopy.
7. Diagnostic laparoscopy.
8. Proctoscopy.
9. Chest X – ray.
10. Intravenous urogram.

Laboratory examination:

- Complete blood count.
- The blood test called CA – 125 is useful in differential diagnosis and in the follow – up of the disease.
- The blood test on levels of lysopholipids (a type of fatty acid).
- Histologic examination of the ovarian specimen is the basic method of diagnoses.

Treatment

Treatment modalities are:

Surgery

- Organ – saving (salvage) operation – removal of the uterus on the side of lesion resection of contralateral ovary, removal of gross omentum, washing and biopsy of the pelvis and diaphragm.
- Extirpation (hysterectomy) of uterus, adnexa and greater omentum in advanced diseases.
- Lymphodissection is managed after standard operation in patients with retroperitoneal lymph node spread and absence of residual tumor in peritoneum.
- Secondary cytoreductive surgery is managed in patients with local recurrences (presence of solitary solid or cysto – solid mobile tumors without dissemination in peritoneum).
- In some cases preoperation chemotherapy is indicated.

In dependence of the extent of residual disease, operations are subdivided into:

- optimal cytoreductive surgery (absence of residual tumor, CA – 125 levels can be elevated);
- suboptimal cytoreductive surgery (residual tumor < 2 cm or residual tumor);
- not – optimal cytoreductive operation (residual tumor > 2cm).

Chemotherapy

Chemotherapy is the most common therapy for patients with advanced disease. Cisplatin derivatives, particularly carboplatin have significant activity. It produces bone marrow suppression with little or no nephrotoxicity, ototoxicity or peripheral neuropathy.

Treatment with two – drug combination achieved a significantly higher response rate.

- Paclitaxel and cisplatin.
- Paclitaxel and carboplatin.
- Cisplatin and cyclophosphamide.
- Carboplatin and cyclophosphamide.
- Docetaxel and cisplatin.

Radiation therapy

Radiation therapy is an adjuvant one for treating patients with tumors not responding to chemotherapy and for patients after primary chemotherapy. This method can be useful for palliative treatment in incurable patients with symptomatic pelvic masses or distant metastases.

Patients with primary and recurrent neoplasias can be managed both by total abdomen irradiation, and irradiation of separate sites (areas).

Radiation therapy efficacy is clearly noticeable one month later, CA – 125 levels usually return to normal 2-3 month after cessation of treatment.

Immunotherapy.

Polyserosites (ascytes or pleurisy) are indicated in patients with Ovarian cancer having recurrent neoplasias or after combined or complex treatment failure.

Complications

Complication of radiation therapy.

- Liver dysfunction.
- Bowel damage.

Complication of chemotherapy.

- Leukemia.
- Bone metastases.
- Central nervous system involvement.
- Ascites.

Prognosis

Tumor residium is very powerful in predicting the therapeutic outcome. There are 3 prognostically distinct subgroups (according to development of recurrences) based on stage of disease, grade of tumor, the amount of residual disease.

Poor – risk patients – stage I and G1.

Moderate risk patients – stage I and II, G2 and G3; stage IIIa and G1.

High risk patients – stage II G3, stages III and IV.

5 – year survival in patients with (OC)
stage I – 80-90% survival.
stage II – 65-70% survival.
stage III - 30%-60% survival.
stage IV – 20% survival.

Questions for self control

Uterine cancer

1. What is uterine cancer?
2. What are the risk factors of uterine cancer?
3. What are the symptoms of uterine cancer?
4. Methods of diagnosis verification of uterine cancer

Cervical cancer

5. What are the risk factors of cervical cancer?
6. What are the symptoms of cervical cancer?
7. What are the patterns of cervical cancer spread?

Ovarian cancer

8. What are the risk factors of ovarian cancer?
9. What is the classification of malignant ovarian tumors?
10. What are the symptoms of ovarian cancer?

Tests (choose the correct option)

1. The major method of uterine cancer diagnosis is:

- a) rectomanoscopy;
- b) CT;
- c) chest X – ray;
- d) aspiration biopsy of the endometrium.

2. The primary method of uterine cancer treatment is:

- a) radiation therapy;
- b) chemotherapy;
- c) surgery;
- d) hormonotherapy.

3. Most common symptom of cervical cancer is

- a) obesity;
- b) weight loss;
- c) bleeding;
- d) low back pain.

4. Metastases usually occur by means of:

- a) lymphatics;
- b) hematogenous;
- c) implantation;
- d) mixed.

5. At ovarian cancer treatment with chemical drugs can be complication:

- a) leukemia, bone metastases;
- b) weight loss;
- c) anorexia;
- d) vomiting;
- e) nausea.

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

PROSTATE CANCER

Incidence

The number of patients with prostate cancer (PC) steadily increases. The widespread use of more efficient diagnostic tests including measurement of prostate – specific antigen (PSA) levels increased greatly the number of patients diagnosed with prostate cancer.

The peak incidence was marked at the beginning of 70th years. In Ukraine prostate cancer incidence was 35.8 cases per 100000 population in 2012 year.

Prostate cancer is the 1st in men. The highest incidence of prostate cancer is in the USA and the lowest is in Asia and Africa. However incidence of PC rises rapidly in Chinese and Japanese immigrants to the USA, it is not so high in China and Japan.

Risk factors

- Age. The incidence of latent carcinoma of the prostate increases with age. 70% of men older than 80 years have different forms of prostate cancer.
- Diet. High – fat diet causes prostate cancer. Diet rich in vegetables (soy) is protective.
- Vitamin D – deficiency.
- Genetic predisposition to develop carcinoma of the prostate cancer has been observed.
- In relatives of patient with prostate cancer, the risk for developing carcinoma of the prostate is more than twice that in control.

Morphologic classification

Most tumors of prostate gland are epithelial (99%), 98% of PC prove to be adenocarcinomas, 2% are squamous cell transitional cell carcinomas.

Gleason's grading system is the most popular grading system.

It recognizes five histological patterns which are assigned grade numbers, and combines the dominant and secondary pattern number into a histologic sum. A numeric representation of anatomic stage was

combined with the histologic score to produce a final Gleason combined score that was most predictive of outcome.

Gleason Scoring System

Pattern I. Closely packed, single, separate, round, uniform glands; well – defined tumor margin.

Pattern II. Single, separate, round less uniform glands separated by stroma up to one gland diameter; tumor margin less well defined.

Pattern III. Single, separate, irregular glands of variable size; enlarged masses with cribriform or papillary pattern; poorly defined tumor margin.

Pattern IV. Fused glands in mass with infiltrating cords, small glands with papillary, cribriform, or solid patterns; cells small, dark, or hypernephroid (clear cells).

Pattern V. Few or no glands in background of masses with comedo pattern; cords or sheets of tumor cells infiltrating stroma.

Evaluation of the histologic grade ('G')

Usually, the grade of the cancer (how different the tissue is from normal tissue) is evaluated separately from the stage; however, for prostate cancer, grade information is used in conjunction with TNM status to group cases into four overall stages.

GX: cannot assess grade

G1: the tumor closely resembles normal tissue (Gleason 2–4)

G2: the tumor somewhat resembles normal tissue (Gleason 5–6)

G3–4: the tumor resembles normal tissue barely or not at all (Gleason 7–10)

This system of describing tumors as "well-", "moderately-", and "poorly-" differentiated based on Gleason score of 2-4, 5-6, and 7-10, respectively, persists in SEER and other databases but is generally outdated. In recent years pathologists rarely assign a tumor grade less than 3, particularly in biopsy tissue. A more contemporary consideration of Gleason grade is:

Gleason 3+3: tumor is low grade (favorable prognosis)

Gleason 3+4 / 3+5: tumor is mostly low grade with some high grade

Gleason 4+3 / 5+3: tumor is mostly high grade with some low grade

Gleason 4+4 / 4+5 / 5+4 / 5+5: tumor is all high grade

Classification of PC by TNM system

Tumor extent (T)

TX Primary tumor cannot be assessed;

T0 No evidence of primary tumor;

Tumor is incidental histologic finding;

T1 Clinically inapparent tumor not palpable or visible by imaging;

T1a Tumor is incidental histologic finding in 5% or less of the total surgical specimen;

T1b Tumor incidental histologic finding in 5% or more of tissue resected;

T1c Digitally unrecognizable neoplasm identified by needle biopsy under transrectal US guidance (e.g. because of elevated PSA);

T2 Palpable tumor limited to the prostate;

T2a Tumor involves half of one lobe or less;

T2b Tumor involves more than half of one lobe;

T2c Tumor involves both lobes;

T3 Tumor extends beyond the prostatic capsule;

T3a Extracapsular extension;

T3b Extracapsular extension, invasion of seminal vesicles;

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles.

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed;

NO No regional lymph node metastasis;

N1 Metastasis in regional lymph nodes.

Distant metastasis (M)

MX Presence of distant metastasis cannot be assessed;

MO No distant metastasis;

M1 Distant metastasis;

M1a Metastasis into lymph nodes which are not regional;

M1b Bone metastasis;

M1c Metastasis into others sites (rectum, seminal vesicles).

Grouping of PC in stages

| | | | | |
|----------|-----|----|----|-------|
| Stage I | T1a | N0 | M0 | G1 |
| Stage II | T1a | N0 | M0 | G2–4 |
| | T1b | N0 | M0 | Any G |

| | | | | |
|-----------|-------|-------|----|-------|
| | T1c | N0 | M0 | Any G |
| | T1 | N0 | M0 | Any G |
| | T2 | N0 | M0 | Any G |
| Stage III | T3 | N0 | M0 | Any G |
| Stage IV | T4 | N0 | M0 | Any G |
| | Any T | N1 | M0 | Any G |
| | Any T | Any N | M1 | Any G |

Routes of spread (Lymphatic, hematogenic spread. Direct extension. Vascular spread).

PC spreads by local invasion, lymphatic and hematogenic routes. Local invasion is a common route of spread beyond the capsule and presents the metastasizing. Tumor penetrates the prostatic capsule and involves bladder, seminal vesicles. Lymphatic metastases most often affect obturator lymph nodes and presacral lymph nodes.

Hematogenic metastases most often affect bones. Metastases to bones have been registered in 80% of patients with prostate cancer as a result of direct invasion of the venous system and systemic dissemination. In the most cases these lesions can be osteoblastic, lytic and mixed ones. Spinal cord, femoral bones, and pelvis, are common sites of metastatic spread. Liver, lung and bone marrow are also common sites of soft tissue metastatic spread.

Clinical presentation

- At early stage prostate cancer is asymptomatic and can be the result of incidental pathologic findings of biopsy and transurethral resection (TRUS) in patients with elevated PSA levels.

In the result of prostate gland increase in volume the symptoms of intravesical obstruction (dysuria, decreased urine stream, residual urine) and irritative symptoms are observed. Urine out flow from kidneys causes their hydronephrosic transformation. Local – spread prostate cancer can squeeze distal portion of rectum, and grow into it. In these cases patients have constipation, tenesmus, rectal bleeding, mucus flow from rectum.

- Bone pain is one of the difficult problems in the management of prostate carcinoma. However some patients have extensive but painless bone involvement. Carcinoma of the prostate produces

prostaglandins – mediator of pain and inflammation. Iliac and genital lymph node lesion develops lymphedema and so leg and genital edema. Cachexia, anemia, bladder bleeding are the result of tumor progression.

- Weight loss.
- Anorexia.
- Extremity pain and edema.

Diagnoses

- History (anamnesis)

Early stage PC_s are diagnosed by:

- rectal palpation – the prostate is located at the outlet of the urinary bladder and is accessible to palpation through the rectum. The accuracy of PC rectal palpation is 30 – 50%. PC can be staged by rectal palpation. In 85% of patients with local prostate cancer and PSA levels 3 – 4 ng/ml tumor can't be measured by palpation.
- Measurement of prostate – specific antigen (PSA) levels and transrectal ultrasonography (TRUS) with prostate biopsy. PSA is a screen protease secreted into the seminal coagulum. It was Wang et al. who secreted glycoprotein (PSA) from men's prostate gland tissue in 1979. PSA is a specific marker for prostatic epithelium, normal or malignant was created by Parsidero et al in 1980.

Biopsy and transurethral resection of the prostate cause elevation of PSA levels. PSA has a 2.2 to 3.2 – day terminal half life. The other cause of PSA level elevation is acute and chronic prostatitis.

- Age related indexes. The upper limit of normal PSA is 4 ng/ml. The age related indexes are: 40 – 49 years (0 – 2.5 ng/ml), 50 – 59 years (0 – 3.5 ng/ml), 60 – 69 years (0 – 4.5 ng/ml), 70 – 79 years (0 – 6.5 ng/ml). PSA increases the detection rate of early – stage and local forms of PC. PSA is not enough sensitive in the detection of latent, focal PC. Patients diagnosed with latent or focal PC have normal PSA levels. At the same time this index is positive in almost 100% of patients with stage T3-4. PC can be at any PSA levels.
- PSA density is PSA concentration to prostate gland volume ratio. It is established by transrectal ultrasonography (TRUS).
- PSA increase velocity is year to year variation in PSA. Increase velocity more than 0.75 ng/ml prompts a prostate biopsy, even if the age related index is normal.

- Free PSA percentage. There are bound and free PSA. The measurement of bound and free PSA helps to differentiate mildly elevated PSA levels characteristic of cancer from elevated levels characteristic of benign prostatic hyperplasia. The lower the ratio of free – to total PSA, the higher the possibility of cancer.

The PSA gene exhibits an 82% homology with H – GK1 and has a similar structure. In the normal prostate and benign prostatic hypertrophy, but not in cancer, PSA and H – GK1 expression correlate. Expression of the PSA gene contains an androgen response element and is regulated by the presence of androgen and other unidentified tissue – specific elements.

So, PSA gene expression increases with puberty and decreases after androgen removal. In blood most PSA is bound to α_1 – antichymotrypsin and is enzymatically inactive. Circulating PSA has a 2.2 to 3.2 day terminal half life, that's why circulating levels reflect the rate of production.

There are other methods of diagnoses:

- Ostioscintigraphy (bone scan or radiographic measurement of osteoblastic lesion).
- Lung X – ray.
- Transrectal ultrasonography (systemic biopsy specimens from transformed zones of prostate gland can be taken under ultrasonographic guidance. One or some hypoechoic areas are commonly associated with PC. TRUS sensitivity in stage assessment is 66%, specificity is 46%.
- MRI.

Screening

One of the screening drawbacks is hyper diagnoses, i.e. detection of the latent forms of cancer that are not biologically significant (not threatening the life). About 40% of men at age of 60 – 70 years have microscopic foci of well differentiated adenocarcinoma. Such tumors < 0.2 – 0.5mm clinically unimportant (latent cancer of no threat to the patient). So the goal of prostate screening is not only the detection of early stage of prostate cancer but diagnoses of forms which are considered threatening to the patient's life.

Taking into account the fact that clinically unimportant prostate cancers (latent cancer) are found in 75 – 100% of cases in men with PSA (0 – 1.9 ng/ml, and sometimes at PCA – 2 – 2.9 ng/ml, urologists should pay attention at the patients with $PSA \geq 3$.

Treatment

Stages T1a – T1b treatment

Stages T1a – T1b as a rule are highly – differentiated not palpable tumors of 0.2 – 0.5 mm volume can be detected at morphological examination of resected prostate tissue. The patients can be carefully watched in case of well differentiated cancer presence in less than 5% of resected tissue.

Most of these tumors are latent cancers, which are clinically unimportant i.e. not threatening the life of the patients.

Stages T1c – T2c treatment

There are three different approaches to T1c and T2c stage treatment: radical prostatectomy, different variants of radiation therapy (external radiotherapy, brachytherapy or their combination) and careful observation. The less healthy and older patients with height – differentiated tumors less than 10 – year remaining life expectancy and with intercurrent disease require observation. Most candidates for radical prostatectomy are younger than patients who are indicated radiation therapy and don't have concomitant pathology. Patients older 70 with 10 – year life expectancy are not indicated radical prostatectomy.

Metastatic PC treatment

Hormonotherapy

The standard method of metastatic prostate cancer management is hormonotherapy.

Most methods of PC endocrine therapy are aimed at serum testosterone level decrease by suppression of testosterone synthesis in testicles and cortex of adrenal gland.

Bilateral orchiectomy is the cheapest and rapid method of getting testosterone castrate levels. Medical castration by analog of luteinizing hormone – releasing hormone (LHRH) agonist is widely used because of

negative psychology effect of surgical castration. Decline of testosterone levels to postcastration values is observed 3 weeks after initiation of (LHRH) agonist administration. Stable "chemical" castration is achieved by subdermal (zoladex 3.6mg) or intramuscular (dypherelin 3.75 mg) injections of long – term depot – form analogs of (LHRH) agonist.

The combination of LHRH agonist analogs with nonsteroid (casodex, flutamide) or steroid (androcure) antiandrogens gives very rapid response and blocks the "flare" after the first administration. Steroidal antiandrogens have also antiandrogen action which inhibits testosterone production according to principle of negative feedback. Combination of surgical and medical castration with nonsteroidal or steroidal antiandrogens is called maximal or total androgen blockade (MAB), because endocrine function of testes – is blocked and action of adrenal gland androgens levels. MAB is recommended to the patients associated with serious cord compression and pain syndrome to achieve the rapid onset of response and blockade of the "flare". Some trials note the effectiveness of monotherapy by antiandrogen casodex at a dose 150mg once daily of the patients who want as long as possible to avoid side effects of castration.

There are limits of hormonal therapy for metastatic prostate carcinoma. Hormone – refractory carcinoma of prostate is proved by elevated PSA levels at castrate testosterone levels and develops usually 24 months after initiation of therapy. Mean survival rates of the patients with hormone – refractory carcinoma is 6 to 12 months.

Chemotherapy

Chemotherapy is the standard method of treating the patients with hormone – refractory carcinoma of prostate. Taxanes are used in chemotherapy. Cytotoxic agents and their combination with inhibitors of different factors of growth are studied as second – line chemotherapy. If chemotherapy fails, the main goal is improvement of patients' quality of life.

External beam radiation

Hemibody external – beam irradiation of the patient with symptomatic bone metastases with radiation dose 20 – 40Gr has been reported to provide relief of pain in 80% of cases. The other

symptomatic method of treatment the patients with bone metastases is the use of radioactive strontium – 89 (89 Sr). Strontium is handled in biologic systems in a fashion similar to calcium parenteral. It accumulates selectively within the blastic bone lesions that are characteristic of carcinoma of the prostate. It is effective in the management of bone pain.

PC patients with bone metastases are administered bisphosphonates (zomet) to lessen the pain and prolong the complication free life period.

Prognoses

Patients with PC have poor prognosis because more than 90% of patients with PC are diagnosed in advanced stages of disease. Radical prostatectomy can provide 15 – year cancer – free survival in patients younger than 70. The survival of patients with PC depends on the stage of disease.

5 – year survival

Stage I – II – 85%.

Stage III – 50%.

Stage IV – 40%.

Questions for self control

1. What is prostate cancer?
2. How is prostate cancer diagnosed?
3. What are the risk factors for prostate cancer?
4. What are the symptoms of prostate cancer?
5. Methods of diagnosis verification.
6. Morphologic classification of prostate cancer.
7. Routes of prostate cancer spread.

Tests (choose the correct option)

1. The highest incidence of PC is in

- a) Asia.
- b) Africa.
- c) USA.
- d) Europe.
- e) Ukraine.

2. The most popular prostate cancer grading system.

- a) Virchow's.
- b) Schnitzler's.
- c) Compression syndrome.
- d) Gleason.

3. Most tumors of prostate gland are

- a) small – cell carcinomas;
- b) epithelial;
- c) basal cell carcinoma;
- d) papillary carcinoma.

4. What is the most common risk factor of PC

- a) cigarette smoking;
- b) exposure to ionizing irradiation;
- c) age;
- d) genetic factors.

5. The diagnoses of prostate cancer

- a) palpation and PSA levels measurement;
- b) biopsy;
- c) MRT;
- d) transrectal ultrasonography.

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

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