1.1 Epidemiology

D.P. Berger, H. Henß

Def: Describes the frequency with which a disease occurs and examines possible links between disease occurrence and risk factors.

Meth:

Terms

- *Incidence:* total number of new cases of a given disease occurring in a population during a defined time interval (e.g., new cases per year)
- *Incidence Rate:* incidence within a given population (e.g., incidence per 100,000 people)
- *Prevalence:* total number of affected members of the population at a set point in time
- *Prevalence Rate:* prevalence within a given population (e.g., prevalence per 100,000 people)
- *Mortality:* total number of disease-related deaths occurring during a defined time interval (e.g., disease-related deaths per year)
- *Mortality Rate:* mortality within a given population (e.g., disease-related deaths per 100,000 people per year)

Risk

Describes the likelihood of an event occurring within a defined time interval, e.g., risk of developing a particular tumor (incidence risk) or risk of dying of a disease (mortality risk).

Risk Factors

Factors contributing to a specific risk. Risk factors for malignant diseases include demographical data (age, sex), geographical distribution, socio-economic factors, environmental factors, and biological parameters ("molecular epidemiology").

Relative Risk (RR)

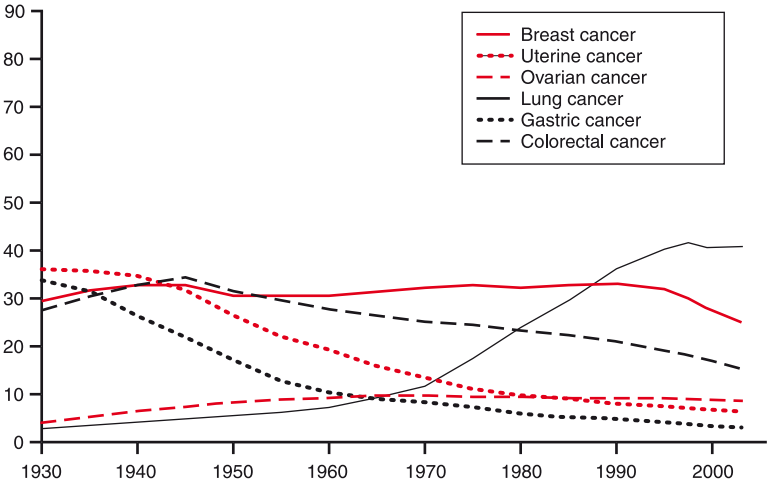
Epidemiological term which compares the risk (e.g., of disease occurrence) within a specific subpopulation ("high-risk group," e.g., smokers) with the average population. A factor > 1.0 represents an increased RR, factors < 1.0 constitute a reduced RR.

Average Age at Which a Disease Occurs

Maximum of the age-specific distribution of cases of a disease.

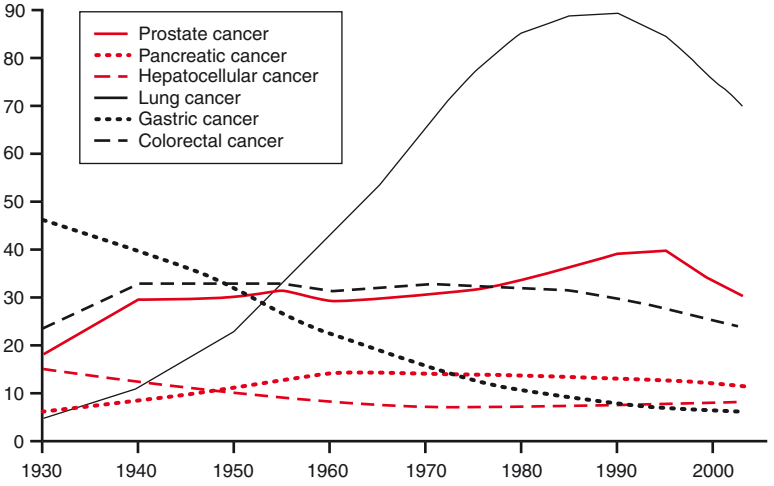
Incidence, age distribution, and gender distribution of each entity are shown in the disease-related chapters (► Chaps. 6.1–8.13). Recent research suggests that 70–80% of all malignant diseases are triggered by certain lifestyle habits or environmental carcinogens. In addition, hereditary factors are of particular importance (► Chap. 1.2).

Development of mortality rates of female patients with solid tumors (USA, 1930–2003, age-adjusted mortality rate per 100,000)



Source: American Cancer Society, Cancer Facts and Figures 2003

Development of mortality rates of male patients with solid tumors (USA, 1930–2003, age-adjusted mortality rate per 100,000)



Ref:

1. American Cancer Society. Cancer Facts and Figures 2003. Atlanta, GA, 2003
2. Jemal A, Siegel R., Ward E et al. Cancer Statistics, 2007. CA Cancer J Clin 2007;57:43–66
3. Lichtenstein P, Holm NV, Verkasalo PK et al. Environmental and heritable factors in the causation of cancer. N Engl J Med 2000;343:78–85
4. Kamangar F, Dores GM, Anderson WF. Patterns of Cancer incidence, mortality, and prevalence across five continents. J Clin Oncol 2006;24:2137–50.

Web:

1.	http://www.cancer.org/	American Cancer Society
2.	http://www.iacr.com.fr/	Intl. Association of Cancer Registries
3.	http://seer.cancer.gov/	NCI SEER Database

1.2 Carcinogenesis, Molecular Tumor Biology

D.P. Berger, U. Martens

Def: Development of malignant diseases is a result of multiple exogenic and endogenic factors. Of pivotal importance is the accumulation of genetic and epigenetic changes leading to the selection of a cell population with malignant phenotype. Characteristics are:

- Unlimited proliferation, immortalization
- Loss of antiproliferative feedback mechanisms, autonomous growth, not dependent on proliferation signals (e.g., autocrine stimulation)
- Loss of ability to induce apoptosis
- Neovascularization
- Metastatic and invasive properties

Pg: The development of a malignant tumor requires several steps (see model of multistep carcinogenesis). Point mutations (single nucleotide changes) or cytogenetic aberrations (e.g., translocation / inversion / deletion) lead to altered activity of genes (e.g., p53, pRB) impacting tumor growth regulation and biology of malignant cells. These can be hereditary ("germline mutation") or spontaneous ("somatic mutation") as a result of multiple factors ("carcinogens" or carcinogenic defects).

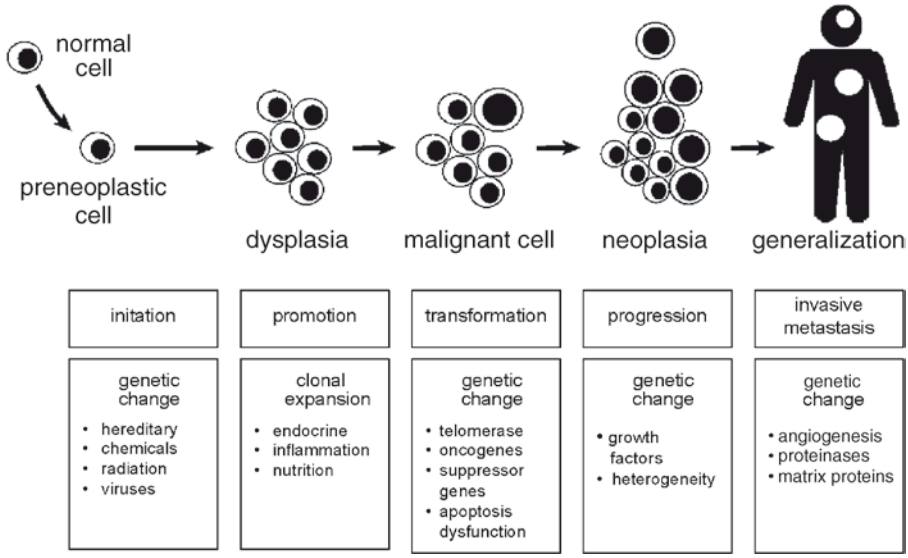
Exogenous Carcinogens:

- Chemicals, drugs
- Ionizing radiation
- Infections (viruses, bacteria, protozoa, particularly chronic infections)

Endogenous Carcinogens:

- Defective DNA repair mechanisms
- Defective regulation of epigenetic events
- Genetic instability

Model of multistep carcinogenesis



Carcinogens and associated human neoplasias

Carcinogen / group	Associated diseases
Alcohol / Tobacco:	
Alcohol	Hepatic carcinoma, head and neck tumors, gastrointestinal tumors
Tobacco	Lung cancer, head and neck tumors, esophageal carcinoma, pancreatic carcinoma, renal cell carcinoma, carcinoma of renal pelvis, bladder carcinoma
Industrial substances and environmental pollutants:	
Aromatic amines	Bladder carcinoma, urinary tract tumors
Arsenic, arsenic compounds	Lung cancer, skin tumors
Asbestos	Lung cancer, mesothelioma
Benzol, styrol, benzene	Acute myeloid leukemia
Benzidine	Bladder carcinoma
Beryllium	Lung cancer
Chloromethyl ether	Lung cancer
Chromium, chromium compounds	Lung cancer, head and neck tumors
Halogenated hydrocarbons	Hepatic carcinoma, urinary tract tumors
Halogenated alkyl, aryl and alkylaryl oxides	Lung cancer, head and neck / gastrointestinal / urinary tract / skin tumors
Wood dust	Tumors of paranasal sinuses
Ionizing radiation	Various solid tumors, leukemias
Isopropanol production	Tumors of paranasal sinuses
Cadmium	Lung cancer
Crude coking plant gases	Lung cancer, head and neck tumors
Nickel and nickel compounds	Lung cancer, head and neck tumors
Nitrosamines	Esophageal carcinoma
Polycyclic hydrocarbons	Lung cancer, scrotal carcinoma, skin tumors
Radon and radon decay products	Lung cancer
Soot, tar, anthrazene	Skin tumors
Quartz dust (silicosis)	Lung cancer
Mustard gas	Lung cancer, head and neck tumors
Trichloroethylene	Renal cell carcinoma
Ultraviolet light (sunlight, UV-B)	Skin tumors, melanoma
Vinyl chloride	Hepatic angiosarcoma

Carcinogens and associated human neoplasias *(continued)*

Carcinogen / group	Associated diseases
Drugs:	
Alkylating agents	Acute myeloid leukemia, bladder carcinoma
Androgenic steroids	Hepatic carcinoma
Diethylstilbestrol (prenatal)	Vaginal adenocarcinoma
Epipodophyllotoxin derivates	Acute myeloid leukemia
Immunosuppressants (azathioprine, cyclosporine)	Non-Hodgkin's lymphomas, skin tumors, sarcomas
Phenacetine	Carcinoma of renal pelvis, bladder carcinoma
Synthetic estrogens	Endometrial carcinoma
Bacteria, viruses, fungi:	
Aflatoxins	Hepatic carcinoma
Chronic hepatitis B, C (HBV, HCV)	Hepatic carcinoma
Epstein-Barr virus (EBV)	Burkitt's lymphoma, nasopharyngeal carcinoma
Helicobacter pylori	Gastric cancer, MALT-lymphoma of the stomach
HIV	Lymphomas, Kaposi's sarcoma
HTLV-1	Adult T-cell leukemia / lymphomas
Human papillomaviruses (HPV)	Cervical / vulvar / anal / penile carcinoma
KSHV / HHV-8	Kaposi's sarcoma, multiple myeloma (?)
Schistosomiasis	Bladder carcinoma

Ref:

1. Bergen AW, Caporaso N. Cigarette smoking. J Natl Cancer Inst 1999;91:1365–75
2. Berrington de Gonzales A, Darby S. Risk of cancer from diagnostic X-rays. Lancet 2004;363:345–51
3. Hahn WC, Weinberg RA. Rules for making tumor cells. N Eng J Med 2002;347:1593–603
4. Jordan CT, Guzman ML, Noble M. Cancer stem cell. N Engl J Med 2006;355:1253–61
5. Lichtenstein P, Holm NV, Verkasalo PK et al. Environmental and heritable factors in the causation of cancer. N Eng J Med 2000;343:78–85
6. Ponder BAJ. Cancer genetics. Nature 2001;411:336–41
7. Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. Nat Med 2004;10:789-99
8. World Health Organisation IARC monographs on the evaluation of carcinogenic risks to humans, 1–74. Lyon, IARC, 1972-2000

Web:

1.	http://www.iarc.fr	Intl. Agency for Research on Cancer
2.	http://www.nlm.nih.gov/pubs/factsheets/ccrisfs.html	Chemical Carcinogen Information
3.	http://ehp.niehs.nih.gov/roc/toc10.html	NIH Report on Carcinogens
4.	http://potency.berkeley.edu/cpdb.html	Carcinogenic Potency Database
5.	http://cancer.gov/cancerinfo/prevention-genetics-causes	Cancer Genetics, NIH
6.	http://AtlasGeneticsOncology.org	Cytogenetics Atlas
7.	http://www.carcinogenesis.com/home/	Journal of Carcinogenesis
8.	http://www.nature.com/nrc/poster/subpathways/index.html	A subway map to cancer

Genetic variations and associated solid tumors

Hereditary syndrome	Gene	Locus	Primary tumor	Associated disease
Li-Fraumeni syndrome	TP53	17p13.1	Breast cancer, sarcomas	CNS tumors, leukemias, lymphomas
Familial adenomatous polyposis (FAP, Gardner's syndrome)	APC,MYH	5q21	Colorectal cancer	Gastric cancer, pancreatic carcinoma, osteomas, medulloblastoma
Hereditary non-polyposis colorectal cancer (HNPCC, Lynch's syndrome)	MSH2,MLH1, PMS1, PMS2, MSH6	2p16, 3p21, 2q32, 7p22	Colorectal cancer	Endometrial / ovarian / hepatic carcinoma, renal carcinoma, glioblastoma
Hereditary diffuse gastric carcinoma	CDH1	16q21-22	Gastric cancer	Breast cancer, colorectal tumors?
Neurofibromatosis type 1	NF1	17q11.2	Neurofibromas	Neurofibrosarcoma, AML, CNS tumors
Neurofibromatosis type 2	NF2	22q12.2	Acoustic neurinoma, meningioma	Gliomas, ependymomas
Wilms' tumor	WT1, WT2	11p13, 11p15	Wilms' tumor (nephroblastoma)	Aniridia, urogenital defects, mental retardation
Hereditary breast cancer type 1, 2	BRCA1, BRCA2	17q21, 13q12	Breast cancer	Ovarian carcinoma, pancreatic carcinoma
Bloom's syndrome	BLM	15q26	Leukemias, lymphomas	Diverse solid tumors, immunodeficiencies
von Hippel-Lindau's (VHL) syndrome	VHL	3p12	Hypernephroid carcinoma	Pheochromocytoma, retinal angiomas, cerebellar hemangiomas
Hereditary papillary renal carcinoma	MeT	7q31	Papillary renal carcinoma	Other solid tumors
Familial melanoma	CDKN2A(p16), CDK4	9p21, 12q13	Melanoma	Pancreatic carcinoma, dysplastic moles
Multiple endocrine neoplasia 1 (MEN 1)	MEN 1	11q13	Islet carcinoma	Parathyroid adenomas
Multiple endocrine neoplasia 2 (MEN 2)	MEN 2 (RET)	10q11.2	Medullary thyroid carcinoma	Pheochromocytomas, hamartomas, parathyroid adenomas
Cowden's syndrome	PTEN, MMAC1	10q23	Breast cancer, follicular thyroid carcinoma	Hamartomas, intestinal polyps, cutaneous lesions
Ataxia telangiectasia (Louis-Bar)	ATM	11q22	Lymphomas	Ataxia, immunodeficiency, breast cancer
Xeroderma pigmentosum	XBD, XPD, XPA	Variable	Skin tumors	Abnormal pigmentation, hypogonadism
Fanconi's anemia	FACC, FACA	9q22, 16q24	AML	Pancytopenia, skeletal defects
Retinoblastoma	RB	13q14	Retinoblastoma	Osteosarcomas
Tuberous sclerosis	TSC1, TSC2	9q34, 16p13	Cutaneous fibroadenomas	Astrocytomas, skin tumors

1.3 Hematopoiesis and Development of Hematological Neoplasia

C.I. Müller, D.P. Berger, M. Engelhardt

Def: Hematopoiesis is the formation of effector cells of the peripheral blood and bone marrow. In the bone marrow, approximately 1×10^{12} cells are formed daily.
Differentiation:

- *Myelopoiesis:* formation of myeloid effector cells (granulocytes, monocytes, macrophages)
- *Lymphopoiesis:* formation of lymphocytic effector cells (T lymphocytes, B lymphocytes)
- *Erythropoiesis:* formation of erythrocytes
- *Thrombopoiesis:* formation of thrombocytes (platelets)
- *Granulopoiesis:* formation of granulocytes (eosinophils, basophils, neutrophils)

Phys:

Location of Hematopoiesis

- Embryogenesis: hematopoiesis in liver → spleen → bone marrow
- Adulthood: bone marrow. In case of medullary insufficiency, liver and spleen can take over hematopoietic function ("extramedullary hematopoiesis")

Regulation of Hematopoiesis

Proliferation and differentiation of stem cells, progenitor cells and effector cells are regulated by hematopoietic growth factors (HGF):

- Stem and progenitor cells: Flt-2 / flk-3 ligand, stem cell factor (SCF)
- Erythropoiesis: erythropoietin, SCF, interleukin-3 (IL-3)
- Thrombopoiesis: thrombopoietin, SCF, IL-3, IL-6, IL-11
- Granulopoiesis: IL-3, granulocyte colony-stimulating factor (G-CSF), GM-CSF
- Lymphopoiesis: Flt-2 / flk-3 ligand, SCF, IL-2, IL-6, IL-7

Effector Cell Characteristics

- *Erythrocytes:* carry oxygen and hemoglobin, diameter 8 µm, biconcave, akaryotic, developmental period 7 days, life span 120 days
- *Thrombocytes:* "platelets," essential for coagulation, size 1–2 µm, granular, basophilic, developmental period 10–12 days, life span of circulating thrombocytes 7–8 days
- *Neutrophil granulocytes:* defense against infections (particularly bacterial infections), ≤ 5 nuclear segments connected by chromatin bridges ("segmented granulocyte"), developmental period 7–10 days, life span of mature neutrophil granulocyte 7–10 h, average production 10×10^9/h, in response to infection up to 500×10^9/h
- *Eosinophil granulocytes:* relevant in allergic and parasitic diseases, two nuclear segments connected by chromatin bridges, eosinophilic cytoplasm
- *Basophil granulocytes:* relevant in allergic and parasitic diseases, two nuclear segments connected by chromatin bridges, rough basophilic cytoplasmic granules
- *Monocytes:* resistance to infection and phagocytosis, nuclear sinuses and loosely structured chromatin, median life span in peripheral blood 20–40 days
- *B lymphocytes:* antibody-mediated immune response, plasmacytic precursors, diameter 7–12 µm, basophilic cytoplasm, central round nucleus with densely structured chromatin
- *T lymphocytes:* cellular immune response, diameter 7–12 µm, basophilic cytoplasm, central round nucleus with densely structured chromatin

Phys:

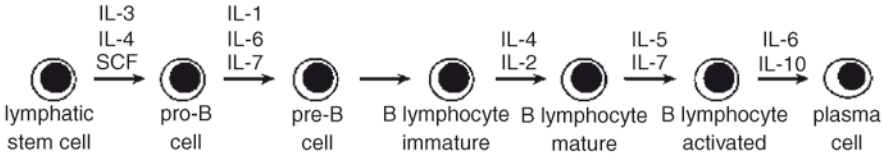
Hematological Neoplasia

Hematologic neoplasms are formed by malignant transformation of cells of certain developmental stages → some characteristics of the neoplastic disease may be aligned with features of the corresponding stage of differentiation, e.g., proliferative activity, surface markers (CD antigens), molecular markers.

Model of hematopoiesis

BFU-E burst-forming unit–erythroid, *CFU* colony-forming unit, *Ba* basophils, *E* erythrocytes, *Eo* eosinophils, *G* granulocytes, *M* monocytes or macrophages, *Meg* megakaryocytes, *NK* natural killer

Example: B-cell development, differentiation, and expression of surface markers (CD antigens). Hematologic malignancies developing at a specific stage of differentiation will carry the given CD antigen expression pattern.



IL Interleukin, *SCF* Stem Cell Factor, *CD* Surface Marker (Cluster of Differentiation ►Chap. 2.5)

Formation of hematological neoplasias on the basis of:

- Erythropoiesis → erythroleukemias (AML M6) (► Chap. 7.1.2)
- Thrombopoiesis → megakaryoblastic leukemias (AML M7) (► Chap. 7.1.2)
- Granulopoiesis → acute myeloid leukemias (► Chap. 7.1.2)
- Lymphopoiesis → lymphomas, lymphatic leukemias (► Chaps. 7.1.1, 7.4, 7.5)

Ref:

1. Akashi K, Traver D, Kondo M et al. Lymphoid development from hematopoietic stem cells. Int J Hematol 1999;69:217–26
2. Baraldi-Junkins CA, Beck AC, Rothstein G. Hematopoiesis and cytokines. Hematol Oncol Clin North Am 2000;14:45–61
3. Broxmeyer HE, Kim CH. Regulation of hematopoiesis in a sea of chemokine family members with a plethora of redundant activities. Exp Hematol 1999;27:1113–23
4. Fey MF. Normal and malignant hematopoiesis. Ann Oncol 2007;18(suppl. 1):i9–i13
5. Gilliland DG, Griffin JD. The roles of FLT3 in hematopoiesis and leukemia. Blood 2002;100:1532–42
6. Hoang T. The origin of hematopoietic cell type diversity. Oncogene 2004;23:7188–98
7. Kondo M, Wagers AJ, Manz MG et al. Biology of hematopoietic stem cells and progenitors: implications for clinical application. Annu Rev Immunol 2003;21:759–806
8. Kyba M, Daley GQ. Hematopoiesis from embryonic stem cells: lessons from and for ontogeny. Exp Hematol 2003;31:994–1006
9. LeBien TW. Fates of human B-cell precursors. Blood 2000;96:9–23

Web:

1. http://www.hematology.org — American Society of Hematology (ASH)
2. http://www.bloodline.net/ — Hematological Education and News
3. http://pathy.med.nagoya-u.ac.jp/atlas/doc/ — Hematology Atlas of the University of Nagoya
4. http://www.hematologyatlas.com/ — Hematology Atlas

1.4 Prevention and Screening

H. Henß

Def: Primary prevention = prevention of tumor development
Secondary prevention = tumor screening
Tertiary prevention = post-treatment follow-up and care to ensure early detection of relapse

Primary Prevention

Def: Successful primary prevention of all malignancies is currently unrealistic for the following reasons:

- Unresolved etiology and pathogenesis of malignant diseases
- Multiple oncogenetic mechanisms of malignant diseases
- Uncertain efficacy of the majority of primary preventive measures (chemoprevention, antioxidant therapy, etc.)

However, epidemiological research suggests that specific measures may reduce the risk of developing certain tumors. Activities with the potential for tumor prevention are:

- Sufficient physical exercise
- Adequate nutrition
- Avoidance of exogenous risk factors (e.g., smoking)

Pg: Primary prevention focuses on definition, recognition, and avoidance of risk factors, which can be genetically determined and/or acquired. Once genetic risk factors have been identified, they can be used to define a high-risk population.

Genetic Risk Factors: Examples (► Chap. 1.2)

- Familial adenomatous polyposis (FAP) and other familial colorectal tumors (HNPCC)
- Familial breast cancer and/or familial ovarian carcinoma (BRCA1, BRCA2)
- Xeroderma pigmentosum

In the presence of genetic risk factors, cancer screening, preventive therapy, and chemoprevention have to be considered.

Acquired Risk Factors Associated with Certain Tumors (► Chap. 1.2)

- *Smoking:* lung cancer, squamous cell carcinoma of the head and neck, breast cancer, pancreatic carcinoma, bladder carcinoma, renal cell carcinoma
- *Alcohol:* squamous cell carcinoma of the head and neck, hepatocellular carcinoma, breast cancer, gastrointestinal tumors
- *Hazardous substances:* lung cancer (e.g., asbestos), nasopharyngeal carcinoma (hardwood dust), bladder carcinoma (tar, solvents)
- *Infections:* hepatocellular carcinoma (hepatitis B / C), cervical carcinoma (papilloma virus, HPV), gastric cancer (*Helicobacter pylori*)
- *Excess exposure to sunlight / UV light:* malignant melanoma, basal cell carcinoma
- *Obesity (esp. postmenopausal):* breast cancer, endometrial carcinoma, prostatic cancer, colorectal cancer

Px: The "European Code Against Cancer" was developed as a source of information for patients. It contains general rules of conduct in order to prevent tumor development.

European Code Against Cancer (2003)

Many aspects of general health can be improved, and certain cancers avoided, if you adopt a healthier life style

1. Do not smoke. If you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers
2. Avoid obesity
3. Undertake some brisk physical activity every day
4. Increase your daily intake and variety of vegetables and fruits: eat at least 5 servings daily. Limit your intake of foods containing fats from animal sources
5. If you drink alcohol, whether beer, wine, or spirits, moderate your consumption to two drinks per day if you are a man and one drink per day if you are a woman
6. Care must be taken to avoid excessive sun exposure. It is specifically important to protect children and adolescents. For individuals who have a tendency to burn in the sun, active protective measures must be taken throughout life
7. Apply strictly regulations aimed at preventing any exposure to known cancer-causing substances. Follow all health and safety instructions on substances which may cause cancer. Follow advice of national radiation protection offices

There are public health programs that could prevent cancers developing or increase the probability that a cancer may be cured

8. Women from 25 years of age should participate in cervical screening. This should be within programs with quality control procedures in compliance with European Guidelines for Quality Assurance in Cervical Screening
9. Women from 50 years of age should participate in breast screening. This should be within programs with quality control procedures in compliance with European Guidelines for Quality Assurance in Mammography Screening
10. Men and women from 50 years of age should participate in colorectal screening. This should be within programs with built-in quality assurance procedures
11. Participate in vaccination programs against hepatitis B virus infection

Other measures

12. See a doctor if you notice a lump, a persistent wound (including inside the mouth), changes in shape, color, or size of a mole, any abnormal bleeding
13. See a doctor if you have persistent symptoms such as a chronic cough or persistent hoarseness, a change in bowel habits / urination, or unexpected weight loss

Chemoprevention

Def: Prevention of tumor development via prophylactic medication.

Th:

Colorectal Tumors

- Retrospective studies demonstrate risk reduction through regular use of acetylsalicylic acid or non-steroidal antiinflammatory drugs (NSAIDs).
- Prospective studies showed decreased numbers of adenomas, but no significant influence on carcinoma-related mortality → General use of acetylsalicylic acid or NSAIDs for the prevention of colorectal tumors is presently not recommended due to the possible side effects.

Breast Cancer

- Positive family history and/or identification of the BRCA-1 and BRCA-2 genes constitute a higher risk. However, the extent of this risk remains uncertain. Recent studies have shown that women carrying the genes have up to an 80% lifetime risk of developing the disease by the age of 80.
- Initial larger studies using tamoxifen in high-risk populations showed a positive influence on the disease risk. Consequently, the US National Cancer Institute (NCI) formulated a recommendation for the prophylactic use of tamoxifen in patients at risk of developing breast cancer. At present, this recommendation is judged controversial as other studies failed to reproduce the initial results or have even shown a negative influence of tamoxifen → ***Outside of studies, tamoxifen use should be limited to clearly defined high-risk populations. Frequent follow-up is required due to the increased risk of endometrial carcinoma.***

Cervical Carcinoma

Vaccination against human papillomavirus type 16 (HPV-16) prevents intraepithelial cervical neoplasias.

Lung Cancer

Two large studies were conducted on the influence of protective substances in high-risk populations:

- ATBC study: administration of alpha-tocopherol (vitamin E) and β-carotene
- CARET study: administration of β-carotene and retinol

Neither study showed any benefit in relation to the occurrence of lung cancer. Instead, mortality was increased in the β-carotene group (higher incidence of bronchial carcinomas and myocardial infarction). Hence, further similar studies were discontinued.

Head and Neck Tumors

Patients with successfully removed head and neck tumors show a reduced incidence of metachronous secondary tumors after prophylactic use of retinoids. However, retinoids appeared to have no influence on relapse frequency or metastasis of the primary tumor.

Xeroderma Pigmentosum

The use of retinoids also had a positive effect in known cases of xeroderma pigmentosum.

Selenium

Clinical studies do not conclusively verify the usefulness of selenium substitution. While substitution is useful in selenium deficient areas (e.g., China), it seems to have no protective effect in areas with sufficient selenium supply (e.g., Germany). Results of current clinical studies remain to be seen.

Secondary Prevention (Cancer Screening)

Def: Cancer screening remains the main focus of prophylaxis. Its benefits are, however, still subject to debate.

- On the one hand, there is definite increase in cure rates and prolonged life expectancy in early stages of tumor development.
- On the other hand, there is lead time bias and diagnosis of asymptomatic tumors which have no influence on life expectancy ("over-diagnosis bias").
- Furthermore, false-positive screening results lead to increased technology-intensive and invasive diagnostic procedures with a higher risk of acute and chronic side effects (exposure to radiation, risk of invasive measures, etc.).

Meth: The following World Health Organization (WHO) criteria are adequate guidelines for screening measures.

WHO criteria for sensible and effective cancer screening programs

- The disease should be an important health problem
- There should be an accepted treatment
- There should be facilities for diagnosis and treatment of the disease
- The disease should have a detectable preclinical phase
- The natural history of the disease should be understood
- A suitable screening test should be available
- The test should be acceptable to the general public
- There should be a generally accepted strategy for determining whom to treat
- The costs generated should be acceptable
- The program should be designed to carry out screening continuously

Px:

Cancer Screening Programs

Cancer screening programs are considered standard medical care for:

- Cervical and endometrial carcinoma → women from 20 years of age
- Breast cancer → women from 30 years of age
- Colorectal cancer → women and men from 45 years of age
- Prostate cancer → men from 45 years of age
- Malignant skin tumors → women from 30 years of age / men from 45 years of age.

International publications have firmly established the benefits of screening for:

- Colorectal cancer
- Breast cancer in postmenopausal women
- Cervical carcinoma

Up to now, the exact benefits of screening for prostate cancer have not been verified by published studies. There is a positive trend toward using mammography to screen for breast cancer in premenopausal women. Screening for malignant melanoma is also recommended, especially given the low costs involved and the importance of early treatment. There are no recommendations for lung cancer and ovarian carcinoma. In both cases, currently published studies do not show any correlation between detection by screening and decreased mortality.

Ref:

1. Boyle P, Autier P, Bartelink H et al. European Code Against Cancer and scientific justification: third version (2003). Ann Oncol 2003;14:973–1005
2. Chlebowski RT, Col N et al. ASCO Technology Assessment of Pharmacology Interventions for Breast Cancer Risk Reduction Including Tamoxifen, Raloxifen and Aromatase Inhibition. J Clin Oncol 2002;20:3328–43
3. Imperiale TF. Aspirin and the prevention of colorectal cancer. N Engl J Med 2003;348:879–80
4. Jordan VC. Chemoprevention of breast cancer with selective oestrogenreceptor modulators. Nat Rev Cancer 2007,7:46–53
5. Key TJ, Allen NE et al. The effect of diet on risk of cancer. Lancet 2002;360:861–68
6. Koutsky LA, Ault KA et al. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med 2002;347:1645–51
7. Kushi LH, Byers T, Doyle C et al. ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity. *CA Cancer J Clin* 2006;56:254–81
8. Smith RA, Cokkinides V, Eyre HJ. Cancer screening in the US, 2007: A review of current guidelines, practies, and prospects. *CA Cancer J Clin* 2007;57:90–104

Web:

1.	http://www.cancerprevention.org/	Cancer Prevention Foundation
2.	http://www.cancerprev.org/	Cancer Detection and Prevention
3.	http://www.cancerpreventionfund.com/	National Cancer Prevention Fund
4.	http://www.preventcancer.com/	Cancer Prevention Coalition
5.	http://www.prevention.cancer.gov	Division of Cancer Prevention (NCI)
6.	http://www.cdc.gov/cancer/az/	Center for Disease Control (CDC)

1.5 Classification of Diseases and ICD System

D.P. Berger, H. Henß

Def: Coded disease classifications using internationally standardized systems allow for world wide investigation of causes of morbidity and mortality. For the classification of diseases and causes of death, the World Health Organization (WHO) has established the "International Classification of Diseases" (ICD). In the case of malignant diseases, it focuses particularly on tumor location. Since 1993, the 10th revision of the ICD (ICD-10) has been in use.
In oncology, two codes are being distinguished: "the location code" (ICD-10) and the "ICD-O" which describes the morphology of a malignant disease ("morphology code"). A definite disease classification is only possible by combining ICD-10 and ICD-O.

Meth: ***ICD-10***
ICD-10 describes 21 categories of diseases and causes of death which are coded using a combination of letters and numbers. Hematological and oncological diseases are classified between "C00" and "D90".

General principles of the international classification of diseases, 10th revision (ICD-10)

Chapter	Blocks	Title
I	A00–B99	Certain infectious and parasitic diseases
II	C00–D48	Neoplasms
III	D50–D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune system
IV	E00–E90	Endocrine, nutritional, and metabolic diseases
V	F00–F99	Mental and behavioral disorders
VI	G00–G99	Diseases of the nervous system
VII	H00–H59	Diseases of the eye and adnexa
VIII	H60–H95	Diseases of the ear and mastoid process
IX	I00–I99	Diseases of the circulatory system
X	J00–J99	Diseases of the respiratory system
XI	K00–K93	Diseases of the digestive system
XII	L00–L99	Diseases of the skin and subcutaneous tissue
XIII	M00–M99	Diseases of the musculoskeletal system and connective tissue
XIV	N00–N99	Diseases of the genitourinary system
XV	O00–O99	Pregnancy, childbirth, and the puerperium
XVI	P00–P96	Certain conditions originating in the perinatal period
XVII	Q00–Q99	Congenital malformations, deformations, and chromosomal abnormalities
XVIII	R00–R99	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified
XIX	S00–T98	Injury, poisoning, and certain other consequences of external causes
XX	V01–Y98	External causes of morbidity and mortality
XXI	Z00–Z99	Factors influencing health status and contact with health services

ICD-10 classification of malignant solid tumors

Code	Tumor location	Code	Tumor location
C00	Lips	C46	Kaposi's sarcoma
C01–02	Tongue	C47	Peripheral nervous system
C03–04	Mouth, gum	C48	Retroperitoneum, peritoneum
C05	Palate	C49	Connective and soft tissue
C06	Cheek	C50	Breast
C07–08	Parotid gland, salivary glands	C51	Vulva, labium
C09	Tonsils	C52	Vagina
C10–11	Naso- / oropharynx	C53	Cervix uteri
C13	Hypopharynx	C54	Corpus uteri
C14	Other sites in lip / oral cavity / pharynx	C55	Other uterine carcinomas
C15	Esophagus	C56	Ovaries
C16	Stomach	C57	Other genital organs, ♀
C17	Small intestine	C58	Placenta
C18	Colon	C60	Penis
C19	Rectosigmoid junction	C61	Prostate
C20	Rectum	C62	Testis
C21	Anus, anal canal	C63	Other genital organs, ♂
C22	Liver	C64–65	Kidney, renal pelvis
C23–24	Gallbladder, biliary tract	C66	Ureter
C25	Pancreas	C67–68	Bladder, urethra
C26	Other digestive organs	C69	Eye
C30	Nasal cavity, middle ear	C70	Meninges
C31	Accessory sinuses	C71	Brain
C32	Larynx	C72	Spinal cord, cranial nerves
C33	Trachea	C73	Thyroid gland
C34	Bronchus, lung	C74	Adrenal gland
C37	Thymus	C75	Other endocrine glands
C38	Heart, mediastinum, pleura	C76	Ill-defined primary sites
C39	Other intrathoracic tumors	C77	Lymph node metastasis
C40–41	Bone, articular cartilage	C78	Thoracic / abdominal metastasis
C43	Melanoma	C79	CNS / skeletal metastasis
C44	Other malignant neoplasms of skin	C80	Disseminated metastasis
C45	Mesothelioma	C97	Multiple primary tumors

ICD-10 classification of hematological neoplasms

Code	Tumor location
C81	Hodgkin's disease
C82	Follicular non-Hodgkin's lymphoma
C83	Diffuse non-Hodgkin's lymphoma
C84	Peripheral and cutaneous T-cell lymphoma
C85	Other non-Hodgkin's lymphoma
C88	Malignant immunoproliferative diseases
C90	Multiple myeloma
C91	Lymphoid leukemia (ALL, CLL)
C92	Myeloid leukemias (AML M1–M4, CML)
C93	Monocytic leukemias (AML M5)
C94	Other leukemias (AML M6, AML M7)
C95	Leukemias of unspecified cell type (AML M0)
D45	Polycythemia vera
D46	Myelodysplastic syndromes
D47	Osteomyelofibrosis
D75.2	Essential thrombocytosis

Ref:

1. WHO. International Classification of Diseases, 10th edn (ICD-10). WHO, Genf, 1996
2. WHO. ICD-0 International Classification of Diseases for Oncology, 3rd edn. WHO, Genf, 2000

Web:

1. http://www.who.int/whosis/icd10/ World Health Organization (WHO)
2. http://www.cdc.gov/nchs National Center for Health Statistics (NCHS) Center for Disease Control (CDC)

1.6 Tumor Classification and TNM System

D.P. Berger, H. Henß

Def:

Tumor classification allows for the categorization of malignancies commensurate with different stages of a disease. The objective is to form defined, distinguishable groups of diagnostic, therapeutic, and prognostic relevance.

Pathological Classification: TNM System

The TNM code is internationally established as the pathological classification of solid tumors. Hematological neoplasias are classified differently (see respective disease entities). For solid tumors, too, other clinically relevant staging systems are sometimes being used in addition to the TNM classification. They are essentially aligned with the TNM code:

- Testicular tumors: Lugano / Royal Marsden / Indiana stages
- Colorectal carcinoma: Dukes stages
- Ovarian carcinoma: FIGO stages
- Small cell lung cancer: limited / extensive disease

Clinical Classifications: AJCC / UICC

Clinical classification (corresponding to stages 0, I, II, III, IV) aids further simplification and unites therapeutically and prognostically similar TNM stages. In general, in situ carcinomas are classified as stage 0 and tumors with evident distant metastasis as stage IV.

Depending on each disease entity, clinical categorization is carried out in accordance with recommendations by UICC (Union Internationale Contre le Cancer), AJCC (American Joint Committee on Cancer), or national organizations.

Meth:

TNM System

Internationally standardized system for the categorization and course documentation of solid tumors. The TNM system is based on a graduated description of tumor size (T), lymph node spread (N), and distant metastasis (M).

General principles of the TNM classification (1992, modified 2002)

Parameter	Categories	General definition[a]
Tumor size	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ (microscopic evidence)
	T1–4	Increasing size / local extension of primary tumor
Lymph node metastasis	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1–3	Increasing involvement of regional lymph nodes
	Detection	s: sentinel lymph node, i: isolated tumor cells, mol: molecular genetic testing
Distant metastasis	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
	Organs involved	ADR: adrenals, BRA: brain, HEP: hepatic, LYM: lymph nodes, MAR: bone marrow, OSS: osseous, PER: peritoneum, PLE: pleura, PUL: pulmonary, SKI: skin, OTH: others

Parameter	Categories	General definition[a]
Histopathological grading	GX	Grade of differentiation cannot be assessed
	G1	Well differentiated
	G2	Moderately differentiated
	G3	Poorly differentiated
	G4	Undifferentiated / anaplastic
Prefixes/suffixes	aTNM	Autoptic classification
	cTNM	Clinical classification
	pTNM	Pathological classification
	rTNM	Recurrent tumors
	yTNM	Classification during/after initial therapy
	T(m)NM	Multiple primary tumors
Resection status	RX	Presence of residual tumor cannot be assessed
	R0	No residual tumor
	R1	Microscopic residual tumor
	R2	Macroscopic residual tumor
Venous invasion	VX	Venous invasion cannot be assessed
	V0	No venous invasion
	V1	Microscopic venous invasion
	V2	Macroscopic venous invasion
Diagnostic certainty	C1	Clinical examination
	C2	Special diagnostic means
	C3	Surgical exploration
	C4	Exhaustive pathological examination
	C5	Autopsy

[a] For disease-specific stage definitions ► Chaps. 8.1–8.13

Ref:

1. Greene FL, Page DL, Fleming ID et al. (eds) AJCC Cancer Staging Handbook. TNM Classification of Malignant Tumors, 6th edn. Springer, New York, 2002
2. Gospodarowicz MK, Miller D, Groome PA et al. The process for continuous improvement of the TNM classification. Cancer 2004;100:1–5
3. Sobin LH, Wittekind C (eds). TNM Classification of Malignant Tumors, 6th edn. Wiley, New York, 2002
4. WHO. International Classification of Diseases, 10th edn (ICD-10). WHO, Genf, 1996

Web:

1. http://www.cancerstaging.org American Joint Committee on Cancer (AJCC)
2. http://www.cancer.gov National Cancer Institute (NCI), with Cancernet
3. http://www.uicc.org Union Internationale Contre le Cancer (UICC)

1.7 Indications for Tumor Therapy

D.P. Berger, H. Henß , R. Engelhardt

Def: Factors determining the indication for tumor therapy are:

- Diagnosis
- General health of the patient
- Tumor stage
- Available methods of treatment
- Goals of treatment
- Patient's wish to be treated

Meth:

Diagnosis

Correct diagnosis is a fundamental prerequisite for antineoplastic treatment:

- Histological or cytological diagnosis is necessary
  Exception: acute emergency situations with clinically certain malignancy
- Pathological diagnosis and clinical diagnosis must be compatible

General Health

Scoring of general performance status by Karnofsky or WHO (► Chap. 1.8)

Tumor Stages

Staging systems (► Chap. 1.6)

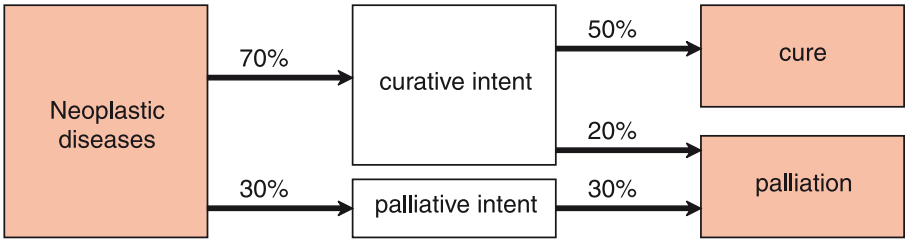
Methods of Treatment

- Surgical treatment
- Drug treatment including chemotherapy
- Radiotherapy
- Interdisciplinary treatment: multimodal antineoplastic therapy including surgery, drug treatment, and radiation. Treatment is planned and performed by specialists cooperating in the involved fields (surgery, medical hematology and oncology, radiotherapy, gynecology, urology, etc.)
- Experimental methods of treatment (e.g., immunotherapy, gene therapy, hyperthermia): use within the framework of clinical trials when conventional treatment is not appropriate

Terms of Interdisciplinary Tumor Therapy

- *Adjuvant Treatment:* postoperative application of additional methods of treatment, aimed at the elimination of residual tumor, or micrometastases, usually via radiotherapy (locally effective treatment) or drug-based tumor therapy (systemically effective treatment)
- *Neoadjuvant Treatment:* preoperative application of additional methods of treatment, aiming at primary reduction of tumor size (to achieve operability) and systemic elimination of disseminated tumor foci

Therapeutic goals and results of treatment



- *Curative treatment:* the objective of therapy is to cure the patient. Primary curative intention justifies intensive methods of treatment (e.g. extensive surgical resection, high-dose chemotherapy, interdisciplinary therapy) despite increased strain on the patient. Treatment must be carried out in accordance with international standards and guidelines
- *Palliative treatment:* aimed at improving the patient's quality of life, controlling symptoms and pain, as well as prolonging the life span. A palliative intention does not normally justify intensive or strenuous methods of treatment. Treatment is particularly adapted to the individual situation of the patient
- *Supportive treatment:* supportive care methods to improve the patient's quality of life and make treatment more tolerable rather than focusing on antineoplastic effectiveness in the narrow sense

The therapeutic objectives in patients with neoplasms may change throughout the course of the disease. If treatment with a primary curative intention fails, the therapeutic focus usually changes to palliative treatment in order to limit further invasive measures.

Ref:

1. Julia H, Rowland JH, Hewitt M, Ganz PA. Cancer survivorship: a new challenge in delivering quality cancer care. J Clin Onc 2006;24:5101–4

Web:

1.	http://www.cancer.org	ACS, Clinical Practice Guidelines
2.	http://www.guideline.gov	National Guideline Clearinghouse (NGC)
3.	http://cancer.gov/cancerinformation	National Cancer Institute (NCI), with Cancernet
4.	http://www.cebm.net	Center for Evidence-Based Medicine

1.8 Performance Status of Tumor Patients ("Performance Status Scales")

D.P. Berger, H. Bertz

Def:

WHO, SAKK, ECOG, Zubrod Definition	Grade	Karnofsky Definition	Index
No symptoms; fully active	0	Normal activity; no complaints; no symptoms of disease	100%
Symptoms; moderate reduction in physical activity and capacity to work; not bed-ridden	1	Slight reduction in normal activity; minor symptoms of disease	90%
		Normal activity only with effort; some symptoms of disease	80%
Unable to work; cares for self; increasing need for assistance, needs to be in bed < 50% of waking hours	2	Cares for self; unable to carry on normal activity or to do active work	70%
		Requires occasional assistance; mainly cares for self	60%
Cannot care for self; requires permanent care or hospitalization; needs to be in bed > 50% of waking hours	3	Requires considerable assistance and frequent medical care	50%
		Disabled; requires special care and assistance	40%
Rapid progression of disease; confined to bed	4	Severely disabled; hospitalization is indicated although death not imminent	30%
		Very sick; hospitalization necessary; active supportive treatment necessary	20%
		Moribund; fatal processes progressing rapidly	10%
Dead	5	Dead	0%

WHO World Health Organization, *SAKK* Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (Swiss Group for Clinical Cancer Research), *ECOG* Eastern Cooperative Oncology Group

Ref:

1. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer 1996;32A:1135–41
2. Garman KS, Cohen HJ. Functional status and the elderly patient. Crit Rev Oncol Hematol 2002;43:191–298
3. Mor V, Laliberte L, Morris JN et al. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. Cancer 1984;53:2002–7
4. Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55

Web:

1. http://www.who.int World Health Organization (WHO)
2. http://ecog.dfci.harvard.edu Eastern Cooperative Oncology Group (ECOG)
3. http://www.fda.gov/cder/cancer Food and Drug Administration (FDA) Oncology Tools

1.9 Response Evaluation in Solid Tumors

D.P. Berger

Def: Clinical response evaluation in individual patients takes into consideration objective parameters as well as subjective criteria:

- Tumor regression in comparison to initial size (degree of remission, "response")
- Remission duration: progression / relapse-free interval
- Survival time: tumor-free survival time and overall survival time
- Toxicity
- Symptom control: regression of tumor-related symptoms (pain, etc.)
- Quality of life: changes in general health

In an overall evaluation of a treatment method within a patient population, the therapeutic response is assessed using similar parameters:

- Response rate: percentage of subjects with tumor remission within a given patient population
- Median remission duration
- Median survival time
- Survival rates (one-year survival rate, five-year survival rate)
- Cost-effectiveness in comparison to other methods of treatment

Meth: ***Response Evaluation in Solid Tumor Therapy***

- Monitoring of tumor size and comparison to pre-treatment baseline
- Definition of tumor progression parameters prior to start of therapy
- Implementation of follow-ups using pre-defined evaluation methods
- Imaging as a prerequisite for objective assessment (x-ray, CT, NMR, photography, etc.)

Class: ***Solid Tumor Response Parameters***

- *WHO Criteria (Miller 1981):* tumor response is evaluated on the basis of measurable tumor manifestations. Tumor size is measured bidimensionally (product of longest diameter × greatest perpendicular diameter, a × b). With multiple tumors, individual products are added up. For the overall response, non-measurable tumor manifestations are also being considered.
- *RECIST Criteria ("Response Evaluation Criteria In Solid Tumors", Therasse 2000):* response evaluation ("best response") only includes measurable tumors ("target lesions"). The evaluation of the tumor size is based on diameter (longest diameter). In case of multiple tumors, individual diameters are added up. Overall response includes the evaluation of target lesions, other non-measurable tumor manifestations ("non-target lesions"), and the occurrence of new tumor manifestations.
- *Measurable Tumor:* any tumor manifestation that can be measured in at least two dimensions.
- *Non-measurable Tumor:* any tumor manifestation which is detectable but can not be measured in two dimensions (e.g., metastasis < 1 cm diameter, lymphangitis carcinomatosa, peritoneal carcinosis, malignant pleural effusion, diffuse metastasis). A "non-measurable" tumor can still be evaluable, e.g., in case of unidimensional expansion (liver enlargement due to metastasis, etc), by the use of clinical parameters (dyspnea, pain, immobility, etc.) or "surrogate" markers (tumor markers, immunoglobulins, etc.).
- *Skeletal Metastasis:* bone metastases are regarded as tumor parameters. However, remission is defined differently (see Table).

Definition of solid tumor remission

Remission status	Abbreviation	Measurable tumor (WHO criteria)	Measurable tumor (RECIST criteria)	Non-measurable tumor or skeletal metastasis
Complete remission	CR	Disappearance of all known disease, confirmed at ≥ 4 weeks[1]	Disappearance of all target lesions, confirmed at ≥ 4 weeks[1]	Disappearance of all target lesions and normalization of tumor markers, confirmed at ≥ 4 weeks[1]
Partial remission	PR	≥ 50% decrease from baseline, confirmed at ≥ 4 weeks[1]	≥ 30% decrease from baseline, confirmed at ≥ 4 weeks[1]	≥ 30–50% decrease from baseline confirmed at ≥ 4 weeks[1]
		No new metastasis	No new lesions	No new metastasis
		No progression of other tumor parameters	No progression of non-target lesions	No increase in other tumor parameters
No change[2] = Stable disease	NC SD	Neither PR or PD criteria met, confirmed at ≥ 4 weeks[1]	Neither PR or PD criteria met, confirmed at ≥ 4 weeks[1]	Target lesion and tumor parameters unchanged compared to baseline, confirmed at ≥ 4 weeks[1]
		No new metastasis	No new lesions	No new metastasis
		No progression of other tumor parameters	No progression of non-target lesions	No increase in other tumor parameters
Progression = Progressive disease	P PD	≥ 25% increase of one or more lesions and/or appearance of new lesions and/or progression of other tumor parameters	≥ 30% increase over smallest sum observed and/or appearance of new lesions and/or progression of other tumor parameters	≥ 25% increase in existent lesions compared to baseline and/or appearance of new lesions and/or appearance of other tumor parameters

[1]Confirmed by 2 tests ≥ 4 weeks apart
[2]"Minor response (MR)": tumor size 50–75% compared to baseline, frequently used in clinical trials

Definition of Therapeutic Response

- Therapeutic response of measurable and non-measurable tumors should be defined separately
- In the presence of several measurable tumor parameters, the single worst parameter is defining the response category. Example: three measurable tumors with partial remission (PR), but occurrence of new lesion ► overall response: "progression."

Remission Duration

- The duration of complete remission (CR) is the time between the first day of documented CR and the first day of detectable progression
- The duration of partial remission is the time between the first day of treatment and the first day of documented progression ("overall response period")

Therapeutic Response in Hematological Neoplasias

There are separate evaluation systems for different types of hematological neoplasias (leukemia, lymphomas). These are, however, based on similar principles:

- Response classification using complete remission, partial remission, stable disease, progression
- In the presence of genetic markers (e.g., Philadelphia chromosome with chronic myeloid leukemia): differentiation between clinical response and "cytogenetic response" (detectability of a cytogenetic or molecular genetic marker)

Survival Time

- "Absolute survival": time between diagnosis / initiation of therapy and death
- "Event-free survival" (EFS): time between diagnosis / initiation of therapy / tumor response and occurrence of new tumor manifestation

Ref:

1. Green S, Weiss GR. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs 1992;10:239–53
2. Jaffe CC. Measures of response: RECIST, WHO, and new alternatives. J Clin Oncol 2006;24:3245–51
3. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16
4. WHO. WHO handbook for reporting results of cancer treatment. WHO, 1979

Web:

1.	http://www.who.int	World Health Organization (WHO)
2.	http://www3.cancer.gov/dip/RECIST.htm	NCI, RECIST Criteria
3.	http://www.swog.org	Southwest Oncology Group (SWOG)

Common Toxicity Criteria (NCI)

Criteria	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Performance status	Fully active	Ambulatory, capable of light work activities	Capable of self-care but not of working, in bed ≤ 50% of time	Capable of only limited self-care, in bed > 50% of time	Completely bedridden
Weight loss	< 5%	5–9.9%	10–19.9%	> 20%	–
Weight gain	< 5%	5–9.9%	10–19.9%	> 20%	–
Leucocytes	≥ 4,000/µl	3,000–3,999/µl	2,000–2,999/µl	1,000–1,999/µl	< 1,000/µl
Neutrophils	≥ 2,000/µl	1,500–1,999/µl	1,000–1,499/µl	500–999/µl	< 500/µl
Lymphocytes	≥ 2,000/µl	1,500–1,999/µl	1,000–1,499/µl	500–999/µl	< 500/µl
Hemoglobin	≥ 11.0 g/dl	10.0–10.9 g/dl	8.0–9.9 g/dl	6.5–7.9 g/dl	< 6.5 g/dl
Platelets	≥ 100,000/µl	75,000–99,999/µl	50,000–74,999/µl	25,000–49,999/µl	< 25,000/µl
Bleeding	None	Mild No transfusion	Moderate 1–2 transfusions	Significant 3–4 transfusions	Severe > 4 transfusions
Prothrombin time	Normal	> 1.0–1.25 × N	> 1.25–1.5 × N	> 1.5–2.0 × N	> 2.0 × N
PTT	Normal	> 1.0–1.66 × N	> 1.66–2.33 × N	> 2.33–3.0 × N	> 3.0 × N
Fibrinogen	Normal	0.75–0.99 × N	0.5–0.74 × N	0.25–0.49 × N	< 0.25 × N
Urea	Normal	< 30.0 mg/dl	30.1–50.0 mg/dl	> 50.0 mg/dl	–
Creatinine	Normal	1.1–1.5 × N	1.6–3.0 × N	3.1–6.0 × N	> 6.0 × N
Hypercalcemia	< 2.65 mmol/l	2.65–2.87 mmol/l	2.88–3.12 mmol/l	3.13–3.37 mmol/l	> 3.37 mmol/l
Hypocalcaemia	> 2.10 mmol/l	1.95–2.10 mmol/l	1.75–1.94 mmol/l	1.51–1.74 mmol/l	≤ 1.50 mmol/l
Hypokalemia	> 3.50 mmol/l	3.01–3.50 mmol/l	2.51–3.00 mmol/l	2.01–2.50 mmol/l	≤ 2.00 mmol/l
Hyponatremia	> 135 mmol/l	131–135 mmol/l	126–130 mmol/l	121–125 mmol/l	≤ 120 mmol/l
Hypomagnesemia	> 1.40 mmol/l	1.11–1.40 mmol/l	0.81–1.10 mmol/l	0.51–0.80 mmol/l	< 0.50 mmol/l
Proteinuria	None	< 3.0 g/l	3.0–10.0 g/l	> 10.0 g/l	Nephrotic syndrome
Hematuria	None	Microhematuria	Macrohematuria	Macrohematuria with clots	Transfusion-dependent hematuria
Bilirubin	Normal	< 1.5 × N	1.6–3.0 × N	3.1–10.0 × N	> 10.0 × N

LVEF left ventricular ejection fraction, *N* normal value, *PTT* partial thromboplastin time, *RR* blood pressure, *SGOT* serum glutamic-oxaloacetic transaminase, *SGPT* serum glutamic-pyruvic transaminase

Common Toxicity Criteria (NCI) (*continued*)

Criteria	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
SGOT / SGPT	Normal	< 2.5 × N	2.6–5.0 × N	5.1–20.0 × N	> 20.0 × N
Alkaline phosphatase	Normal	< 2.5 × N	2.6–5.0 × N	5.1–20.0 × N	> 20.0 × N
Hyperglycemia	≤ 115 mg/dl	116–160 mg/dl	161–250 mg/dl	251–500 mg/dl	> 500 mg/dl, ketoacidosis
Hypoglycemia	≥ 65 mg/dl	55–64 mg/dl	40–54 mg/dl	30–39 mg/dl	< 30 mg/dl, shock
Amylase	Normal	≤ 1.5 × N	1.6–2.0 × N	2.1–5.0 × N	> 5.0 × N
Nausea	None	Mild Normal food intake	Moderate Reduced food intake	Severe No oral food intake	Life-threatening
Vomiting	None	Mild, 1 × /day	2–5 × /day	6–10 × /day	> 10 × /day, life-threatening
Mucositis	None	Erythema, mild symptoms Normal food intake	Erythema Painful ulcers Solid food intake	Painful ulcers Liquid intake	Life-threatening Parenteral nutrition No oral intake
Diarrhea	None	2–3 × /day	4–6 × /day Moderate cramps	≥ 7 × /day Incontinence, severe cramps	Life-threatening Hospital admission required
Obstipation	None	Mild	Moderate Laxative use	Pronounced, subileus	Ileus, obstruction Life-threatening
Arrhythmia	None	Asymptomatic No treatment	Symptomatic No treatment	Symptomatic Treatment necessary	Life-threatening, ventricular tachycardia, fibrillation
Cardiac ischemia	None	Non-specific T wave flattening, asymptomatic	Asymptomatic ST-T segment changes	Angina pectoris without signs of infarction	Myocardial infarction
Cardiac function	Normal	Asymptomatic LVEF 50–59%	Asymptomatic LVEF 40–49%	Symptomatic LVEF 20–39%	Severe or refractory insufficiency LVEF < 20%
Pericardium	Normal	Asymptomatic effusion	Pericarditis	Symptomatic effusion, tap necessary	Pericardial tamponade, emergency tap necessary

LVEF left ventricular ejection fraction, *N* normal value, *PTT* partial thromboplastin time, *RR* blood pressure, *SGOT* serum glutamic-oxaloacetic transaminase, *SGPT* serum glutamic-pyruvic transaminase

Common Toxicity Criteria (NCI) (*continued*)

Criteria	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hypertension	None	Transient, RR diastole ↑ by > 20 mmHg RR > 150/100 mmHg	Recurrent / persisting, RR diastole ↑ by > 20 mmHg RR > 150/100 mmHg	Requiring treatment	Hypertensive crisis
Hypotension	None	Mild orthostatic dysregulation No treatment	Fluid-substitution necessary (< 24 h)	Inpatient treatment necessary (≥ 24 h)	Shock, life-threatening Organ failure
Pulmonary function	> 90% of baseline value, normal	76–90% of baseline value, mild symptoms	51–75% of baseline value, exertional dyspnea	26–50% of baseline value, resting dyspnea	< 25% of baseline value, complete bed rest required
pO_2	> 85 mmHg	71–85 mmHg	61–70 mmHg	51–60 mmHg	≤ 50 mmHg
pCO_2	≤ 40 mmHg	41–50 mmHg	51–60 mmHg	61–70 mmHg	> 70 mmHg
Thrombosis / phlebitis	None	–	Superficial thrombophlebitis	Deep vein thrombosis	Pulmonary embolism, venous occlusion
Injection site reaction	Normal	Mild pain, pruritus, erythema	Moderate pain, swelling, phlebitis, inflammation	Ulcer, necrosis, surgical treatment necessary	–
Skin reaction, erythema, systemic	Normal	Asymptomatic erythema or scattered maculopapular efflorescences	Dense efflorescences, pruritus, erythema, desquamation	Generalized maculopapular alterations, strong desquamation	Exfoliative or ulcerative dermatitis
Hand-foot syndrome	None	Minimal alterations, no pain	Painful alterations, function maintained	Painful alterations, defective function	–
Alopecia	None	Moderate patchy alopecia, visible	Complete alopecia	–	–
Allergy	None	Intermittent chills, temperature < 38°C	Urticaria, chills, temperature > 38°C, mild bronchospasm	Bronchospasm, serum sickness, parenteral treatment	Anaphylactic reaction
Tiredness (fatigue)	None	Mild	Moderate, daily activities restricted	Severe, pronounced reduction of activities	No activities possible

LVEF left ventricular ejection fraction, *N* normal value, *PTT* partial thromboplastin time, *RR* blood pressure, *SGOT* serum glutamic-oxaloacetic transaminase, *SGPT* serum glutamic-pyruvic transaminase

Common Toxicity Criteria (NCI) (*continued*)

Criteria	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Fever	None	< 38°C	38.1–40°C	> 40°C for < 24 h	> 40°C for > 24 h, hypotension
Febrile neutropenia	None	–	–	Existent	Life-threatening, sepsis
Infection	None	Mild infection Not requiring treatment	Moderate infection Oral antibiotics	Major infection Intravenous antibiotics	Life-threatening, sepsis
Somnolence	Normal	Mild somnolence	Moderate somnolence	Pronounced somnolence, stupor	Coma
Confusion	Normal	Transient confusion, disorientation, attention deficit	Confusion, loss of orientation, attention deficit	Confusion, delirium	Life-threatening, hospital admission necessary
Sensory function	Normal	Mild paresthesia Deep tendon reflexes ↓	Moderate paresthesia, objective impairment	Severe paresthesia Loss of function	Complete loss of function
Motor function	Normal	Mild subjective weakness without function impairment	Mild verified weakness without significantly impaired function	Verified weakness with function impairment	Life-threatening paralysis
Cerebellar / ataxia	Normal	Mild dyscoordination or dysdiadochokinesia	Intention tremor, dysmetria, nystagmus, blurred speech	Ataxia	Cerebellar necrosis, loss of function
Mood	Normal	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal
Pain	None	Mild No treatment necessary	Pronounced Treatment necessary	Severe, morphine application necessary	Intractable
Degustation	Normal	Change of taste, normal nutrition	Loss of taste, restricted nutrition	–	–
Vision	Normal	Mildly decreased	Moderately decreased	Symptomatic, subtotal loss of vision	Blindness
Hearing	Normal	Asymptomatic, only audiometric verifiable impairment	Tinnitus, mild subjective hypacusis	Symptomatic hypacusis, corrigible with hearing aid	Deafness, irreversible

LVEF left ventricular ejection fraction, *N* normal value, *PTT* partial thromboplastin time, RR blood pressure, *SGOT* serum glutamic-oxaloacetic transaminase, *SGPT* serum glutamic-pyruvic transaminase

Ref:

1. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf 1999;20:109–17
2. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, management. Lancet 2000;356:1255–9
3. Hesslewood SR. European system for reporting adverse reactions to and defects in radiopharmaceuticals: annual report 1999. Eur J Nucl Med 2001;28:2–8
4. Pirmohamed M, Breckenridge AM, Kitteringham NR et al. Adverse drug reactions. BMJ 1998;316:1295–8
5. Trotti A, Colevas AD, Setser A et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176–81
6. Vincent C. Understanding and responding to adverse events. N Engl J Med 2003;348:1051–6

Web:

1. http://ctep.cancer.gov/reporting/ctc.html NCI Common Toxicity Criteria
2. http://ecog.dfci.harvard.edu/~ecogdba/general/common_tox.html ECOG Common Toxicity Criteria
3. http://www.accessdata.fda.gov/scripts/cder/onctools/toxicity.cfm FDA, Common Toxicity Criteria

1.11 Assessing the Quality of Life of Tumor Patients

S. Fetscher, H. Bertz

Def: There is no standardized definition of "quality of life". The definition suggested by the WHO describing "health" as "complete physical, psychological and social well-being" largely corresponds to the popular-medical understanding of the term "quality of life."
The following components of quality of life can be distinguished:

- Physical condition
- Psychological condition
- Social interaction
- Functioning in the everyday life, behavioral components

Meth: Quality of life evaluation is based on patient self-assessment (usually questionnaire), structured interview procedures and outside assessment by relatives or medical personnel.

Methods of Assessing the General Quality of Life

- Short-form 36 (SF-36), standard method for non-oncological questions
- Affect-balance scale
- Munich Quality of Life-Dimensions List
- Nottingham Health Profile (NHP)
- Lancaster Quality of Life Profile
- Sickness Impact Profile (SIP)
- Oregon Quality of Life Questionnaire
- International Quality of Life Assessment-Group Profile

Special Methods of Quality of Life Assessment in Hematology / Oncology

- EORTC Questionnaire (EORTC QLQ-C30), standard method for oncological assessment in Europe
- Functional Assessment of Cancer Treatment (FACT), standard method for oncological assessment in the USA
- Rotterdam Symptom Checklist (RSCL)
- Quality of Life in Cancer Scale
- Lung Cancer Symptom Scale

IMPORTANT: It is a common misunderstanding that the Karnofsky Index or ECOG Score can be used for quality of life assessment (Chap. 1.8). Both methods are used for the evaluation of a patient's general physical health which is only one component of quality of life. In an individual case, a low Karnofsky index (poor general health) can go hand in hand with a good quality of life and good general health can coincide with poor quality of life.

Ind: Quality of life assessment is particularly indicated in treatment studies or in the framework of modern quality management. In clinical research, implementation of quality of life measures is being increasingly demanded by ethics commissions and institutional review boards.
Quality of life assessment is mandatory with:

- Comparative trials on supportive therapy
- Multicentric phase III trials aimed at establishing new therapeutic standards
- Trials in geriatric oncology
- Trials of palliative therapy

Quality of life assessment with established methods (e.g., EORTC Questionnaire)—especially when used for the evaluation of new methods of therapy—has the following objectives:

- With only small differences in remission and survival data, improved quality of life may determine the choice of treatment
- Clear basis for assessing effects and side effects of a particular treatment
- Improvement of operational aspects and quality of tumor treatment and individual patient care.

- Clearly defined criteria for palliative treatment in patients with advanced malignancies, where toxic experimental therapies are not justified. Once life expectancy is limited, aspects of quality of life need to lead medical and therapeutic decision-making.

Ref:

1. de Haes J, Curran D, Young T et al. Quality of life evaluation in oncological clinical trials – the EORTC model. Eur J Cancer 2000;36:821–5
2. Giesler RB, Williams SD. Opportunities and challenges: assessing quality of life in clinical trials. J Natl Cancer Inst 1998;90:1498–9
3. Holzner B, Bode RK, Hahn EA et al. Equating EORTC QLQ–C30 and FACT–G scores and its use in oncological research. Eur J Cancer 2006;42:3169–77

Web:

1.	http://www.fda.gov	Food and Drug Administration (FDA)
2.	http://www.nci.nih.gov	National Cancer Institute (NCI)
3.	http://www.eortc.be/home/qol/	European Organization for Research and Treatment of Cancer (EORTC), "Quality of Life Web Site"
4.	http://www.isoqol.org/	International Society for Quality of Life Research

1.12 Evidence-based Medicine (EBM), Guidelines and Quality Management

H. Henß

Def: "Evidence-based medicine" (EBM) describes the implementation of diagnostic and therapeutic methods which are based on assured knowledge (evidence), putting purpose and benefit of the respective method second. This is particularly important when several different methods are under consideration.

Class: The evidence of clinical information is classified corresponding to the reliability of the underlying trials. Depending on the way data were obtained, different levels of evidence can be distinguished. Prospective randomized trials including control groups imply the highest reliability.

Levels of evidence according to standard of knowledge

Level of evidence	Definition
1	Evidence obtained from at least one properly designed randomized controlled trial
2	Evidence obtained from well-designed controlled trials without randomization
3	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
4	Evidence obtained from case series with or without intervention
5	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

EBM does not imply that only methods based on controlled randomized studies are legitimate. However, decision making should be based on the highest available level of evidence in each case.

Standards and Guidelines in Oncology

Def: Standards and guidelines, especially on the basis of assured evidence, are designed to support medical decision making in order to guarantee high quality healthcare. Guidelines are:

- Systematically developed tools which help decide on medically adequate approaches to diagnosis and therapy of certain diseases
- Consensus of several experts from various disciplines ("interdisciplinary guidelines") which was developed using defined, transparent procedures
- Scientifically established and practical recommendations for action
- Orientation guides, from which deviation is acceptable in justified circumstances

Objectives of Guidelines and Standards:

- Securing and improving the health care of the population
- Motivation to apply medical procedures that are scientifically established and economically appropriate
- Information about necessary and established medical procedures with regard to special health risks and disorders
- Reduction of undesirable fluctuation of quality in medical care

Class:

Characteristics of Standards

Standards are classified according to their reliability:

- Recommendations: describe options of acting and omission. Of minor normative nature and little scientific evidence.
- Guidelines: systematically developed tools which help decide on medically adequate approaches to specific problems. Science-based practical orientation guides ("action pathways") from which deviation is acceptable in justified cases
- Directives: code of conduct which is approved by a legally authorized institution, set out in writing, and published; legally binding for the legal and judicial area of a specific institution; non-compliance is punished by specific sanctions

IMPORTANT: Directives have to, guidelines should, and recommendations may be observed.

Quality Management

Def:

"Quality" describes all characteristics of a product / service with regards to its ability to satisfy defined and required needs. It comprises:

- Structural quality (financial, technical, and personnel equipment)
- Process quality (here: quality of diagnostic and therapeutic measures, organization, and supervision of treatment procedures)
- Quality of outcome (quality of achieved results by diagnosis and therapy)

"Quality management" describes a dynamic process of continuous evaluation and optimization of all diagnostic and therapeutic measures. "Quality assurance" in the narrow sense merely ascertains compliance with once-defined standards. However, medicine in general and hematology / oncology in particular are subject to constant progress. Therefore, quality management is the preferred option.

Meth:

Quality management results from continuous processes:

- Quality analysis (measuring and registration of deficits)
- Quality improvement (adjustment to expected norms)

Quality is measured by indicators (e.g., treatment associated toxicity; remission rates, survival times, quality of life). Prerequisites are clearly defined indicators that are measured by consistent methods.

Benchmarking

Continuous improvement of quality ("total quality management", TQM) describes the regular comparison of different hospitals or departments by the means of pre-defined indicators. It can initiate development and introduction of new procedures and / or lead to abandonment of obsolete practices. The two most important "parameters" are the patient and the respective disease course.

Gap Analysis

Defective processes hinder smooth diagnosis and therapy. Usually, only a small number of flaws gives rise to a multitude of disruptions ("Single point of failure"). Errors should therefore be listed according to the frequency of their occurrence ("Pareto Diagram") before initiating a "reform." That way, the most significant defects can be detected and adequate measures necessary for their elimination can be decided upon swiftly.

Good Clinical Practice (GCP)

GCP describes the execution of clinical procedures on the basis of tested and approved standard methods ("standard operating procedures"; SOP). GCP is of major importance with complex high-risk procedures (e.g., chemotherapy) and was initially developed for the conduct of clinical trials (► Chap. 3.7).

Ref:

1. Ayanian JZ, Crischilles EA, Wallace RB et al. Understanding cancer treatment and outcomes: the Cancer Care Outcomes Research and Surveillance Consortium. J Clin Oncol 2004;22:2992–6
2. Ray-Coquard I, Philip T, de Laroche G et al. A controlled before-after study: impact of a clinical guidelines program and regional cancer network organization on medical practice. Br J Cancer 2002;86:313–21
3. Schneider EC, Epstein AM, Malin JL et al. Developing a system to assess the quality of cancer care: ASCO's National Initiative on Cancer Care Quality. J Clin Oncol 2004;22:2985–91
4. Vardy J, Tannock IF. Quality of cancer care. Ann Oncol 2004;15:1001–6

Web:

1. http://www.cebm.net Evidence-Based Medicine, Oxford
2. http://www.guideline.gov National Guideline Clearinghouse (NGC)
3. http://cochrane.org/docs/ebm.htm Cochrane Library, Reviews for EBM

1.13 Electronic Media

D.P. Berger

Def: Electronic media, especially the internet, provide an opportunity to rapidly distribute and access current data. This advantage has led to an increased amount of information on up-to-date studies, treatment concepts, and scientific results being online available to doctors and patients.
According to recent studies, there are 12.5 million online searches daily worldwide on health relevant topics. About 40% of tumor patients use the internet to gather information about their disease and approximately 2.3 million patients suffering from a malignant disease have access to the internet, especially in Europe, Asia, and North America.

Meth: The table below lists websites relevant to the hemato-oncological field. We would like to point out that we cannot assume any responsibility for the contents of the listed pages and explicitly distance ourselves from content which is of a non-medical nature or not in accordance with the current state of the art or ethical standards. This list is not exhaustive. It emphasizes websites which have been continuously updated over recent years. Examples are:

"Cancer Topics" (www.cancer.gov/cancertopics)

Up-to-date information by the National Cancer Institute (NCI), Washington, USA:

- Epidemiology, diagnosis, and treatment of hematological and oncological diseases
- Monthly review and updating of the disease-related databases
- Database of worldwide therapy studies
- Information on new treatment approaches and cytostatics
- Information on supportive care
- Separate information resources for doctors and patients

PubMed (www.ncbi.nlm.nih.gov/pubmed)

Comprehensive literature database of the National Center for Biotechnology Information (NCBI) of the National Library of Medicine (NLM). Access to over 10 million manuscripts with abstracts. Includes Medline and several other databases. Search function with excellent access to relevant information.

Hematology / oncology online

Provider / contents	Website
International organizations:	
AACR, American Assoc. for Cancer Research	http://www.aacr.org
ACS, American Cancer Society	http://www.cancer.org
AJCC, American Joint Committee on Cancer	http://www.cancerstaging.org
ASCO, American Society of Clinical Oncology	http://www.asco.org
ASH, American Society of Hematology	http://www.hematology.org
BMDW, Bone Marrow Donors Worldwide	http://bmdw.org
DFCI, Dana Farber Cancer Institute, Harvard	http://www.dfci.harvard.edu
Duke Comprehensive Cancer Center	http://cancer.duke.edu
EACR, European Assoc. for Cancer Research	http://eacr.org
ECOG, Eastern Cooperative Oncology Group	http://www.ecog.dfci.harvard.edu
EORTC, European Organisation for Research and Treatment of Cancer	http://www.eortc.be
ESMO, European Society of Medical Oncology	http://www.esmo.org

Hematology / oncology online *(continued)*

Provider / contents	Website
ESO, European School of Oncology	http://www.cancerworld.org
FDA, Food and Drug Administration	http://www.fda.gov
FECS, Federation of European Cancer Societies	http://www.fecs.be
FHCRC, Fred Hutchinson Cancer Research Center	http://www.fhcrc.org
IACR, International Association Cancer Registries	http://www.iacr.com.fr
IARC, International Agency for Research on Cancer	http://www.iarc.fr
MASCC, Mult. Assoc. Supportive Care in Cancer	http://www.mascc.org
MD Anderson Cancer Center	http://www.mdanderson.org
MSKCC, Memorial Sloan-Kettering Cancer Center	http://www.mskcc.org
NCCN, Natl Comprehensive Cancer Network	http://www.nccn.org
NCI, National Cancer Institute, USA	http://www.cancer.gov
"Oncolink", Univ. Pennsylvania Cancer Center	http://oncolink.upenn.edu
SEER, Surveillance Epidemiology End Results	http://seer.cancer.gov
SWOG, Southwest Oncology Group	http://www.swog.org
Telescan, Netherlands Cancer Institute	http://telescan.nki.nl
UICC, Union Internationale Contre le Cancer	http://www.uicc.org
WHO, World Health Organization	http://www.who.int
General information:	
NCI "Cancer Topics"	http://www.cancer.gov/cancertopics
Cancer Information Network	http://www.cancernetwork.com
FDA Oncology Tools	http://www.fda.gov/cder/cancer
Medline Plus	http://www.nlm.nih.gov/medlineplus
NCCN Clinical Practice Guidelines Oncology	http://www.nccn.org
Medscape Hematology Oncology	http://medscape.com/hematology-oncologyhome
Blood Line	http://www.bloodline.net/
Hematology Atlas, Sao Paulo	http://www.hematologyatlas.com
Hematology Atlas, Nagoya	http://pathy.med.nagoya-u.ac.jp/atlas/doc/atlas.html
Disease-specific information:	
Leukemia and Lymphoma Society	http://www.leukemia.org/
Lymphoma Information Network	http://www.lymphomainfo.net
International Myeloma Foundation	http://myeloma.org
Brain Tumor Society	http://tbts.org
Brain Tumor Association	http://www.abta.org/
National Breast Cancer Foundation	http://nationalbreastcancer.org

Hematology / oncology online *(continued)*

Provider / contents	Website
National Breast Cancer Coalition	http://natlbcc.org
Lung Cancer Online	http://lungcanceronline.org
Lung Cancer	http://lungcancer.gov
Colorectal Cancer Network	http://www.colorectal-cancer.net
Kidney Cancer Association	http://www.nkca.org/
Prostate Cancer	http://www.prostate.com
American Prostate Society	http://www.ameripros.org/
National Prostate Cancer Coalition	http://www.4npcc.org
Prostate Cancer Foundation	http://www.prostatecancerfoundation.org
Prostate Health Directory	http://www.prostatehealthdirectory.org
The Virtual Prostate	http://www.virtualprostate.com
TCRC, Testicular Cancer Resource Center	http://www.comed.com/Prostate
Management of Cancer Pain Guidelines	http://tcrc.acor.org
Carcinogens	http://ehp.niehs.nih.gov.roc
Information on pharmaceuticals:	
Drug Information Network	http://www.druginfonet.com/
Medline Plus Drug Information	http://www.nlm.nih.gov/medlineplus
Cytokine Database	http://www.copewithcytokines.de/
Chemfinder Database	http://chemfinder.cambridgesoft.com/
Dose Calculation of Cytostatics	http://www.meds.com/DChome.html
Literature / journals / information:	
PubMed, National Library of Medicine	http://www.ncbi.nlm.nih.gov/pubmed
History of Biomedicine	http://wwwihm.nlm.nih.gov/
Blood	http://www.bloodjournal.org
CA – A Cancer Journal for Clinicians	http://caonline.amcancersoc.org
Cell	http://www.cell.com
Journal of Clinical Oncology	http://www.jco.org
Journal of the National Cancer Institute	http://jncicancerspectrum/oupjournals.org
The Lancet	http://www.thelancet.com/
Nature	http://www.nature.com
Nature Medicine	http://www.nature.com/nm
Nature Reviews Cancer	http://www.nature.com/nrc
The New England Journal of Medicine	http://www.nejm.org/
Science	http://www.sciencemag.org
Seminars in Hematology	http://www.seminhematol.org
Seminars in Oncology	http://www.seminoncol.org

Hematology / oncology online *(continued)*

Provider / contents	Website
Search engines / other medical servers:	
Google	http://www.google.com
Yahoo	http://www.yahoo.com
Hotbot	http://www.hotbot.com
Dogpile	http://www.dogpile.com
CNN Health News	http://www.cnn.com/health
Cancer News	http://www.cancernews.com
Medscape	http://www.medscape.com
Healthgate	http://www.healthgate.com
Medical Matrix	http://www.medmatrix.org
Reuters Health	http://www.reutershealth.com
WebMD	http://www.webmd.com
DocCheck	http://www.doccheck.com

Ref:

1. Casali P, Licitra L, Tondini C et al. START: a European state-of-the-art on-line instrument for clinical oncologists. Ann Oncol 1999;10:769–73
2. Eysenbach G. The impact of the internet on treatment outcomes. CA Cancer J Clin 2003;53:355–71

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