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Imaging of Complications and Toxicity following Tumor Therapy

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Part I

Basics of Toxicity of Tumor Therapies

Chemotherapy and Targeted Therapy

Florian Lordick and Ulrich Hacker

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Abstract

A precise knowledge of antineoplastic drugs is an indispensable basis for the care of patients with cancer. The mechanisms of action and resistance, cross-resistance patterns, pharmacodynamics and pharmacokinetics, pharmacological interaction, and last but not least potential adverse effects should be part of this knowledge. As contemporary cancer care requires interdisciplinary and multiprofessional structures, the radiologist is an important and integral part of the oncological treatment team. He has several key roles. Besides the determination of an accurate clinical staging which is the basis for all treatment recommendations, he evaluates the response to anticancer treatment and defines the remission status following treatment. Importantly, he assesses acute and long-term treatment toxicities, both having a tremendous impact on patients' safety and quality of life. This article summarizes the principles of medical anticancer treatment and outlines the major side effects associated with drug classes and specific antineoplastic compounds.

Abbreviations

2-CDA	2-Chlordeoxyadenosine
5-FU	5-Fluorouracil
6-MP	6-Mercaptopurine
6-TG	6-Thioguanine

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ACNU	Nimustine
ADL	Activity of daily living
AE	Adverse event
ALK	Anaplastic lymphoma kinase
AMSA	Amsacrine
AraC	Cytosine arabinoside
ARDS	Acute respiratory distress syndrome
BCNU	Carmustine
bcr/abl	Breakpoint cluster region protein/ Abelson murine leukemia viral oncogene homolog 1
CCDP	Cisplatin
CCNU	Lomustine
CD	Cluster of differentiation
c-KIT	Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DNA	Deoxyribonucleic acid
DTIC	Dacarbazine
EGFR	Epidermal growth factor receptor
EML4	Echinoderm microtubule-associated protein-like 4
HDAC	Histone deacetylase
HER2	Human epidermal growth factor receptor 2
ILD	Interstitial lung disease
mTOR	Mammalian target of rapamycin
MTX	Methotrexate
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
PD-1	Programmed cell death protein 1
PDL-1	Programmed cell death ligand 1
PET	Positron emission tomography
PlGF	Placental growth factor
PRES	Progressive reversible encephalopathy syndrome
RAF	Rapidly accelerated fibrosarcoma
SOC	System Organ Class
TKI	Tyrosine kinase inhibitor
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
VP-16	Etoposide
WHO	World Health Organization

1 Basic Principles of Medical Anticancer Therapy

Besides the locally active treatment modalities (surgery and radiation therapy), drug therapy is the third important column of anticancer treatment. Applied via the bloodstream, medical therapy can hit not only the primary tumor but also lymphatic and hematogenous disseminated tumor cells and metastases.

"Cytotoxic drug" denominates a compound that inhibits cell division and kills cells. By its effects on nucleic acid formation, DNA synthesis and repair, and protein synthesis and by the inhibition of particular protein functions that are associated with survival, proliferation, and migration, these drugs exert antiproliferative cytostatic effects or cytotoxic effects as programmed cell death (apoptosis), cell destruction (necrosis), and induction of senescence. Of note, all these effects do not only occur in neoplastic tumor cells but can alter also cells of the healthy tissue, depending on the susceptibility of particular organs to the cytotoxic drug effects. Therefore, cancer chemotherapy has transitioned from the use of cytotoxic drugs to the era of agents with an apparent selectivity for a cancer-specific target (Phelps and Sparreboom 2014). However, targets which are completely specific for cancer cells seem to be rare. And even if such characteristics exist, like the Philadelphia chromosome translocation in chronic myeloid leukemia coding for the cancer-specific bcr/abl tyrosine kinase (Heisterkamp et al. 1985), drugs hitting that target do not work absolutely target specific and do have an impact on functional structures of healthy tissue cells as well.

A classification of anticancer treatment into classical cytostatic or cytotoxic chemotherapy, antihormonal therapy, monoclonal antibody treatment, or treatment with tyrosine kinase inhibitors has historic reasons and appears arbitrary as the cell biological effects of those therapies are pleiotropic and have a great overlap. A certain relevance lies in the discrimination of the mostly non-cancer selective classical cytotoxic treatment ("chemotherapy") and the so-called selective targeted treatment forms like antihormonal therapy, therapeutic

antibodies, and kinase inhibitors. The therapeutic index of classical cytotoxic drugs like alkylating agents is often smaller than that of biologically targeted forms of therapy (Fig. 1).

Classical cytotoxic drugs have different mechanisms of action which are outlined in Fig. 2.

Hanahan and Weinberg described the hallmarks of cancer in a previous landmark article that was updated in 2011. These hallmarks include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Conceptual progress in the last decade has added two emerging hallmarks of potential generality to this list – reprogramming of energy metabolism and evading immune destruction. The "tumor microenvironment" that consists of apparently normal cells adds to the complexity of current tumor characteristics which forms the basis for contemporary drug development and targeted treatment of cancer (Fig. 3) (Hanahan and Weinberg 2011).

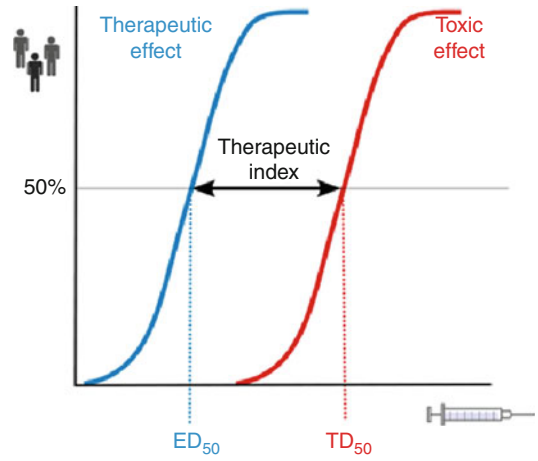

Fig. 1 The concept of therapeutic index refers to the relationship between toxic and therapeutic doses. This pharmacodynamic parameter is relevant to clinical practice because it determines how safe or toxic a drug is. Both ED50 and TD50 are calculated from dose-response curves, which represent the frequency with which each dose of drug elicits the desired response or toxic effect in the population. The dose required to cause a therapeutic effect (positive response) in 50 % of a population is the ED50. The dose required to produce a toxic effect in 50 % of the studied population is the TD50 (Redrawn from Craig and Stitzel (2003))

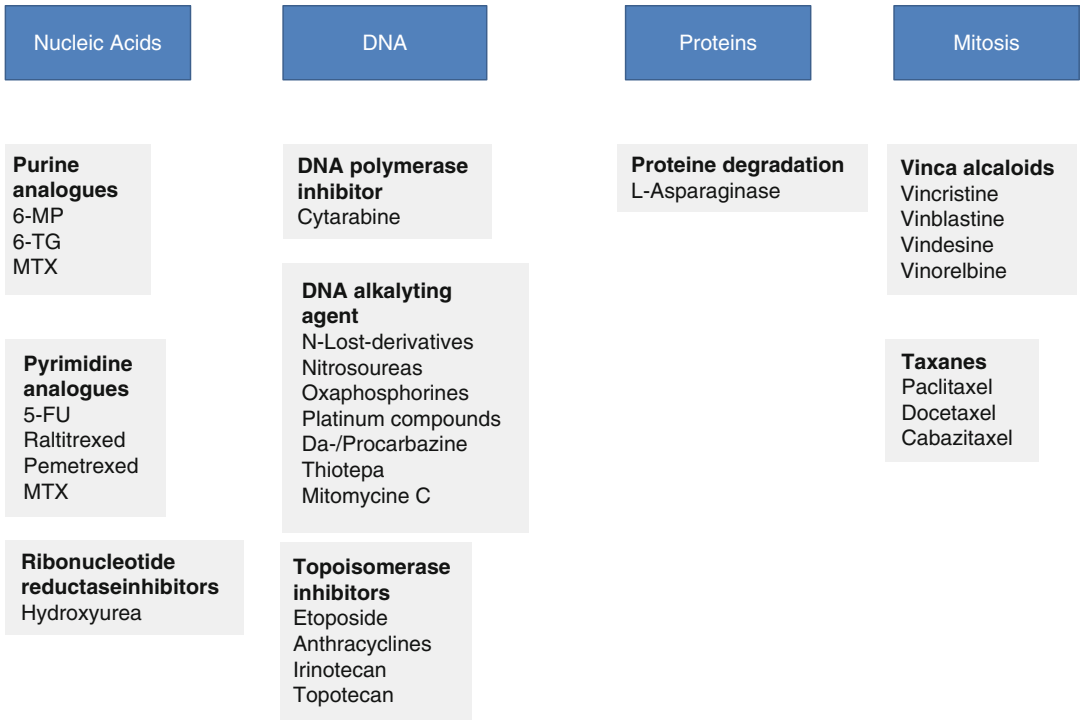

Fig. 2 Target structures of classical cytotoxic drugs: *DNA* deoxyribonucleic acid, *MTX* methotrexate, *5-FU* 5-fluorouracil, *6-MP* 6-mercaptopurine, *6-TG* 6-thioguanine

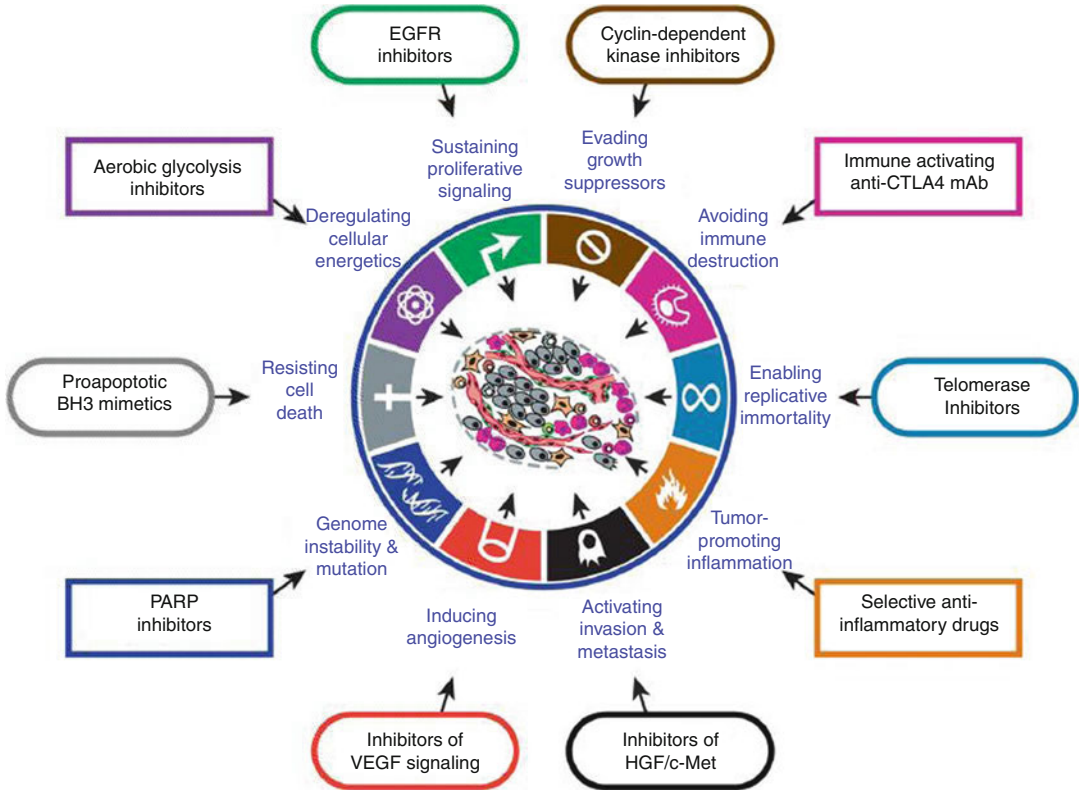

Fig. 3 The hallmarks of cancer (Redrawn from Hanahan and Weinberg (2011)) are the basis for contemporary drug development and targeted anticancer treatment

2 Definitions of Anticancer Drug Therapy

2.1 Mono- Versus Combination Therapy

In principle, combination chemotherapy has advantages over monotherapy due to additive or multiplicative effects of tumor cell kill. Primary or secondary resistant tumor cell clones can be eradicated or suppressed by different mechanisms of action. Ideally, combinations have the following features:

- The combined agents are equally effective.
- Lack of cross-resistance.
- Different mechanisms of action.
- Additive or synergistic mechanisms of action.
- No overlapping toxicities.

For most combinations, this ideal situation does not exist. Especially with regard to side effects, some addition of toxicity must always be accepted when combinations are used.

2.2 Induction Chemotherapy

Induction chemotherapy is used when at the time of diagnosis no acceptable therapeutic alternative exists. Induction chemotherapy shall bring the cancer into a state of better therapeutic options. The goal is "the induction" of an optimal remission, which is at best a "complete remission." High treatment intensities are usually necessary for an optimal induction. Therefore, the probability of inducing adverse effects is usually high.

2.3 Consolidation Therapy

The consolidation therapy shall provide the eradication of clinically occult residual tumor. It shall improve the rate of true complete remissions. Thereby, consolidation shall increase the chances of cure or increase the duration of response.

2.4 Maintenance Therapy

Maintenance therapy, in its classical sense used in the treatment of hematological malignancies like acute leukemia, follows consolidation and shall eradicate or control further residual tumor cells, e.g., those that – due to kinetic resistance – were not yet eradicated by the previous treatment. Maintenance therapy can increase the chance of cure or prolong the time interval until further tumor progression. The latter goal is nowadays often chosen in the palliative treatment of solid tumors when a remission has been achieved by a more intensive treatment period preceding maintenance.

2.5 Perioperative (Neoadjuvant and/or Adjuvant) Chemotherapy

Neoadjuvant (also primary or preoperative) therapy is a treatment in patients with localized or locoregional tumor extension in which the application of local treatment alone (operation or radiation therapy) may lead to an unsatisfactory outcome. Neoadjuvant chemotherapy is applied to reduce the extent of surgery (e.g., in breast cancer, where size reduction of large tumors allows for more breast-conserving surgery following neoadjuvant chemotherapy) and to increase the chances of cure (like in gastric or muscle invasive bladder cancer). In some cancers (e.g., osteosarcoma and Ewing sarcoma), postoperative treatment is tailored on the basis of the achieved response during neoadjuvant therapy.

The goal of adjuvant chemotherapy is the eradication of subclinical metastases ("micrometastases") following primary local treatment (operation or radiation therapy). The clinical goal of treatment is to increase the cure rate.

Accepted indications for perioperative chemotherapy are shown in Table 1. As increased cure rates are the goal of neo-/adjuvant chemotherapy, optimal dose intensity is necessary and some toxicity must be accepted. On the other hand, treatment safety is of utmost importance as patients may survive with the operation alone. In addition, long-term side effects should be avoided as they may lead to a significant impairment of quality of life of cancer survivors; alter physical, cognitive, and social functioning; and may even induce secondary diseases (cancers, leukemia, organ dysfunctions, cardiovascular diseases, etc.) leading to a negative impact on life expectancy.

Table 1 Examples for tumors with an established indication for perioperative (neoadjuvant or adjuvant) therapy

Breast cancer
Ovarian cancer
Esophageal cancer
Gastric cancer
Pancreatic cancer
Colon cancer
Rectal cancer
Lung cancer
Testicular cancer
Urothelial cancer
Ewing sarcoma
Osteosarcoma
Rhabdomyosarcoma

2.6 Palliative Therapy

Palliative chemotherapy is a treatment intended to prolong life, to control symptoms, and to augment quality of life. In case of symptomatic disease, more intensive induction treatment regimens are often applied. For a further stabilization of the tumor, most often less intensive monotherapies are regarded as standard of care. Treatment-emergent side effects must be carefully weighed against potential treatment benefits.

3 Classification of Anticancer Drugs

The classification of anticancer drugs can follow different criteria. Traditionally, the World Health Organization (WHO) chose the mechanisms of action (e.g., alkylating agent) and the origin of compounds (e.g., antitumor antibiotics) as their leading criteria for classification. Table 2 groups the compounds predominantly according to their mechanisms of action.

4 Classification of Treatment Toxicity

Side effects of medical treatment have been classified according to uniform criteria as long as the drug is applied within a clinical study. Internationally, the so-called Common Toxicity Criteria (CTC) or the newer Common Terminology Criteria for Adverse Events (CTCAE) as developed and published by the National Cancer Institute (NCI, Bethesda, USA) are most commonly used. Meanwhile, these criteria have been well implemented into clinical practice and proved useful. Therefore, thorough oncologists and multidisciplinary teams use it outside of clinical studies in routine cancer care. The current version of CTCAE V4.03 can be downloaded from the Internet (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

Table 2 Classification of anticancer drugs according to their mechanisms of action and biochemical properties

Drug class	Group	Compound
Alkylating agent	N-lost-derivatives	Bendamustine
		Busulfan
		Chlorambucil
	Nitrosourea derivatives	Nimustine (ACNU)
		Carmustine (BCNU)
		Lomustine (CCNU)
	Oxaphosphorines	Cyclophosphamide
		Ifosfamide
		Trofosfamide
	Platinum derivatives	Cisplatin (CDDP, DDP)
		Carboplatin
		Oxaliplatin
	Tetrazines	Dacarbazine (DTIC)
		Temozolomide
	Aziridines	Thiotepa
	Others	Amsacrine (AMSA)
		Estramustinphosphate
		Procarbazine
		Treosulfan
Antibiotics	Anthracyclines	Daunorubicin
		Doxorubicin
		Epirubicin
		Idarubicin
	Anthracenedione	Mitoxantrone
	Others	Actinomycin-D
		Bleomycin
		Mitomycin C
Alkaloids	Podophyllotoxin derivative	Etoposide (VP-16)
	Vinca alkaloids	Vinblastine
		Vincristine
		Vindesine
		Vinorelbine
	Taxanes	Cabazitaxel
		Docetaxel
		Paclitaxel
	Camptothecin derivatives	Irinotecan
		Topotecan

Table 2 (continued)

Drug class	Group	Compound
Antimetabolite	Antifolates	Methotrexate (MTX)
		Pemetrexed
	Purine analogues	6-Mercaptopurine (6-MP)
		6-Thioguanine (6-TG)
		Fludarabine
		2-Chlordeoxyadenosine (2-CDA)
	Pyrimidine analogues	5-Fluorouracil (5-FU)
		Capecitabine
		Clofarabine
		Cytosine arabinoside (AraC)
		Gemcitabine
	RNR inhibitor	Hydroxyurea
DNA demethylation	Demethylating agents	Azacytidine
		Decitabine
Protein degradation	Enzyme	L-asparaginase
Aromatase inhibition	Nonsteroidal inhibitors	Anastrozole
		Letrozole
	Steroidal inhibitor	Exemestane
Other hormonal therapies	Antiandrogens	Abiraterone
		Bicalutamide
		Flutamide
		Nilutamide
	Antiestrogen	Fulvestrant
	Gestagens	Medroxyprogesterone acetate
		Megestrol acetate
	Selective estrogen receptor modulators	Raloxifene
		Tamoxifen
Immune modulators	Cytokines	Interferon alpha
		Interleukin 2
	IMIDs	Lenalidomide
		Thalidomide
		Pomalidomide
	Immune checkpoint inhibitors	Ipilimumab
		Lambrolizumab
Monoclonal antibodies	CD20 antibodies	Rituximab
		Ofatumumab
	CD30 antibody-toxin conjugate	Brentuximab vedotin
	CD33 antibody	Gemtuzumab ozogamicin
	CD52 antibody	Alemtuzumab
	EGFR antibodies	Cetuximab
		Panitumumab
	HER2 antibodies	Trastuzumab
		Pertuzumab
	HER2 antibody-toxin conjugate	Trastuzumab emtansine
	VEGF antibody	Bevacizumab
	VEGF recombinant fusion protein	Aflibercept
	VEGFR2 antibody	Ramucirumab

(continued)

Table 2 (continued)

Drug class	Group	Compound
Tyrosine kinase inhibitors	Bcr/abl	Imatinib
		Dasatinib
		Nilotinib
	cKIT	Imatinib
	EGFR	Afatinib
		Erlotinib
		Gefitinib
	HER2	Lapatinib
	Histone deacetylase (HDAC)	Romidepsin
		Vorinostat
	mTOR	Temsirolimus
		Everolimus
	Multiple kinases	Axitinib
		Nintedanib
		Pazopanib
		Regorafenib
		Sorafenib
		Sunitinib
	Proteasome	Bortezomib
		Carfilzomib
	RAF	Vemurafenib
	Smoothened receptor (hedgehog signaling)	Vismodegib
	Somatostatin receptors	Octreotide
		Lanreotide

Compounds are listed with their generic names. Where appropriate, commonly used abbreviations are listed in parentheses

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for *adverse event (AE)* reporting. A grading (severity) scale is provided for each AE term. *System Organ Class (SOC)*, the highest level of the reporting hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). Within each SOC, adverse events are listed and accompanied by descriptions of severity (grade).

An AE is any unfavorable and unintended sign (including an abnormal laboratory or imaging finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

Grade refers to the severity of the AE. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline (Table 3). Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.

5 Specific Toxicities Associated with Anticancer Treatment

All organ systems can be subject to treatment-emergent toxicities.

With classical cytotoxic treatment, myelosuppression (neutropenia, thrombocytopenia, and anemia) is a common side effect. Between 80 and 100 % of all patients undergoing chemotherapy have some grade of myelosuppression leading to

Table 3 Toxicity grades according to the "Common Terminology Criteria for Adverse Events" (CTCAE) reporting system provided by the National Cancer Institute, Bethesda, USA

Grade	Severity
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (ADL)[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to an adverse event

A semicolon indicates "or" within the description of the grade

[a]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b]Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

alterations of the differential blood counts. Severity and duration depend of course on the applied cytotoxic drug and schedule as well as additional risk factors, like age and general health status. In case of neutropenia, patients are at particular risk of acquiring infections. Febrile neutropenia is an emergency situation during antineoplastic treatment. It requires immediate clarification and start of empiric antibiotic treatment. In most cases (except low-risk neutropenia in otherwise unimpaired and compliant patients), this should be done following hospitalization, and intravenous broad-spectrum antibiotics should be given (Klastersky and Paesmans 2013). In more than two thirds of patients, the focus of febrile neutropenia remains unknown, but pulmonary infections, bloodstream infections, urinary infections, infections of the skin and soft tissues, as well as infections of the upper aerodigestive tract should be excluded by appropriate clinical, paraclinical, and radiological diagnostics.

Apart from myelosuppression, non-hematological adverse events are common and need to be well known by the treatment team. Table 4 outlines a selection of substance- and group-specific non-hematological toxicities of anticancer drugs.

Our expectation was that with the introduction of new, more specific and biologically targeted drugs, the efficacy of anticancer treatment would increase, while the side effects would decrease. This hope was desperately disappointed (Niraula et al. 2012). International investigators analyzed all randomized controlled trials evaluating agents approved for the treatment of solid tumors by the US Food and Drug Administration between 2000 and 2010. Odds ratios were computed for three end points of safety and tolerability: treatment-related death, treatment discontinuation related to toxicity, and grade 3 or grade 4 adverse events (AEs). These were then pooled in a meta-analysis. Correlations between these end points and the hazard ratios for overall survival and progression-free survival were also assessed. The investigators came to the conclusion that new anticancer agents that lead to improvements in time-to-event end points also increase morbidity and treatment-related mortality. The balance between efficacy and toxicity may be less favorable in clinical practice because of selection of fewer patients with good performance status and limited comorbidities. Patients' baseline health characteristics should be considered when choosing therapy.

With the use of targeted therapies, novel side effects have emerged that are closely related to the specific mechanisms of action of the respective drug. Targeted therapies in general block certain signaling pathways that play important roles in promoting tumor cell survival and proliferation or interfere with stromal cells like vascular endothelial cells to inhibit tumor angiogenesis or with immune cells to modify antitumor immune responses. Monoclonal antibodies and tyrosine kinase inhibitors (TKI) represent the drug classes that are most commonly used for targeted cancer therapy. Furthermore, specific intracellular signaling checkpoints can be blocked by chemical compounds (i.e., mTOR inhibitors). Another group of drugs targets immune function to improve host anticancer immunity. CTLA-4 antibodies are used to enhance T-cell co-stimulation,

Table 4 Selection of substance and group-specific non-hematological toxicities of anticancer drugs

Substance/group	Typical adverse effect
Alemtuzumab	Opportunistic infection
Anthracyclines/mitoxantrone	Cardiomyopathy, cardiac arrhythmia
Aromatase inhibitors	Bone and joint pain, osteoporosis
Bevacizumab	Arterial hypertension, proteinuria, impaired wound healing, gut perforations, bleeding
Bleomycin	Pulmonary toxicity, lung fibrosis
Bortezomib	Neuropathy
Busulfan	Pulmonary toxicity, veno-occlusive disease
Cetuximab/panitumumab	Acneiform exanthema, allergic reactions
Chlorambucil	Pulmonary toxicity, lung fibrosis
Cytarabine	Central nervous toxicity (especially high-dose AraC leads to cerebellar alterations)
Docetaxel	Finger- and toenail alterations, edema, neuropathy, taste alterations
Erlotinib/gefitinib	Pneumonitis, acute respiratory distress syndrome (ARDS)
Fluoropyrimidines	Diarrhea, stomatitis, hand-foot syndrome, cardiotoxicity (arrhythmias, heart burn, myocardial infarction)
Imatinib	Edema, skin rash
Irinotecan	Diarrhea, cholinergic syndrome
Methotrexate	Central nervous toxicity, hepatic and pulmonary toxicity, nephrotoxicity in case of inadequate renal elimination
Mitomycin C	Hemolytic-uremic syndrome, pulmonary toxicity
Sunitinib/pazopanib/sorafenib/regorafenib	Arterial hypertension, hand-foot syndrome, thyroid disorders
mTOR inhibitors (everolimus, temsirolimus)	Arterial hypertension, pneumonitis, mucositis, erythema, hand-foot syndrome, hyperlipidemia
Nitrosoureas	Pulmonary toxicity, lung fibrosis, renal toxicity
Oxazaphosphorines (cyclophosphamide, ifosfamide)	Urothelial toxicity, renal toxicity, central nervous toxicity (reversible psychosyndrome with high-dose ifosfamide)
Paclitaxel/docetaxel	Neuropathy, allergic reactions, onycholysis
Platinum compounds	Renal impairment (cisplatin), ototoxicity (cisplatin), neuropathy (oxaliplatin > cisplatin >> carboplatin)
Tamoxifen	Thromboembolic events
Trastuzumab/pertuzumab/lapatinib	Cardiac toxicity
Vinca alkaloids	Neuropathy

and drugs targeting the PD-1/PD-L1 pathway have been developed to block inhibitory immune checkpoints.

An overview of key side effects can be found in Table 2. Specific side effects resulting in pathological radiological findings are shortly summarized in the following section.

Agents Targeting the Epidermal Growth Factor Receptor (EGFR): The monoclonal antibodies (cetuximab, panitumumab) are used for the treatment of RAS wild-type metastatic colorectal cancer, while TKI (gefitinib, erlotinib, afatinib) represent a standard of care in the treatment of EGFR-mutated non-small cell lung cancer (NSCLC) patients. Skin toxicities occur with high frequency in both groups of drugs. In contrast, interstitial lung disease (ILD) represents a rare complication, and the mechanism is not fully understood. Disruption of the alveolar epithelial function however may play a role. Based on this, the frequency of ILD is higher in smokers and in patients with preexisting lung disease (Ando et al. 2006).

Agents Targeting Her-2: Chemotherapy combined with monoclonal antibodies (trastuzumab, pertuzumab) represents a treatment standard in

Her2-positive breast cancer and in Her2 gastric cancer (trastuzumab). The TKI lapatinib targeting EGFR and Her2neu is approved for the treatment of breast cancer. An important side effect of this class of drugs is cardiotoxicity that is related to the expression of Her2 on cardiomyocytes. Mechanistically, Her2 signaling results in sarcomere stability and initiates repair processes that are important to counteract toxic stress (Tocchetti et al. 2012).

Agents Targeting Tumor Angiogenesis: The monoclonal antibody bevacizumab binds vascular endothelial growth factor (VEGF), and the fusion construct aflibercept binds VEGF and placental growth factor (PlGF). Both drugs are used in combination with chemotherapy for the treatment of metastatic colorectal cancer. Additionally, a large number of TKI targeting VEGF receptors and other receptors are in clinical use for the treatment of a wide variety of cancer types (Table 2). Hypertension and proteinuria represent common side effects of VEGF-targeting therapy. Furthermore, the rate of thromboembolic complications is increased. Other side effects are related to impaired tissue repair capacity and comprise gastrointestinal pneumatosis perforations and the formation of fistulas (Shinagare et al. 2012). Overall, bleeding is a rare side effect. However, frequent bleeding complications have resulted in the exclusion of the use of bevacizumab in squamous cell carcinoma of the lung. Progressive reversible encephalopathy syndrome (PRES) is a very rare (≤0.1 %) but severe neurological complication that has been reported in patient treatment with bevacizumab or aflibercept (Seet and Rabinstein 2012). The disruption of cerebrovascular endothelial cell signaling is related to the disruption of cerebrovascular autoregulation preferentially in the posterior circulation of the brain. Finally, pancreatitis (sunitinib, sorafenib, pazopanib) and acalculous cholecystitis (sunitinib) have been reported in the literature on a casuistic basis.

Anaplastic Lymphoma Kinase (ALK) Inhibitors: ALK inhibitors are used for the treatment of NSCLC harboring specific genomic rearrangements (EML4-ALK). Pneumonitis has been reported with the use of the ALK inhibitor crizotinib and symptoms started within two months of treatment. The underlying mechanisms are not yet clarified.

RAF-Targeting Agents: RAF-targeting agents include the multi-TKI sorafenib for the treatment of renal cell and hepatocellular cancer as well as vemurafenib and dabrafenib, which are used for the treatment of melanoma harboring the B-Raf mutation V600E and other B-Raf mutations. An increase in the occurrence of cutaneous squamous cell carcinomas has been reported, and nodular panniculitis (Monfort et al. 2012) may result in increased radiotracer uptake during 18F-FDG positron emission tomography (PET).

Agents Targeting Mammalian Target of Rapamycin (mTOR) and Targeted Immune Modulators: These agents (everolimus, temsirolimus) are used for the treatment of breast and renal cancers and pancreatic neuroendocrine tumors. Mucositis and aphthous mucosal lesions are common side effects. Additionally, interstitial pneumonitis is an important side effect of this class of drugs with up to 36 % of patients showing any pulmonary abnormalities during treatment (Duran et al. 2014).

Ipilimumab is a novel targeted immune modulator that interacts with CLTA-4, thus fostering co-stimulatory function to improve host antitumor immune response. Due to immune function deregulation, autoimmune-related side effects like enterocolitis and hypophysitis may occur. Additionally, unspecific lymph node enlargement and soft tissue changes like myositis or fasciitis as well as retroperitoneal fat opacities due to lymphocyte infiltration may interfere with treatment response assessment (Bronstein et al. 2011).

As examples of "new toxicities" emerging from biologically selective targeted drugs, Fig. 4 displays a perforation at the rectosigmoid level that occurred during treatment of metastatic colorectal cancer with the anti-VEGF antibody bevacizumab. Another patient who was also treated for metastatic colorectal cancer received the monoclonal anti-EGFR antibody cetuximab plus chemotherapy and developed a grade 3 skin rash during weeks 4–6 of this combined treatment (Fig. 5).

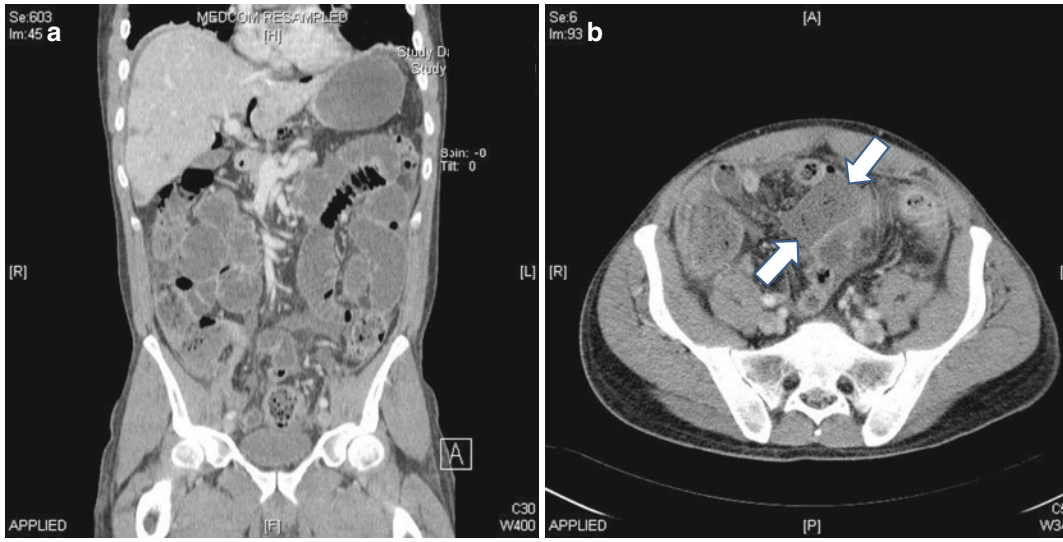

Fig. 4 Gut perforation leading to an ileus and peritonitis, emerging from a pararectal abscess in a patient with colorectal cancer with simultaneous liver and lung metastases. (**a**) Is illustrating the coronary section through the abdomen; (**b**) is illustrating a transversal section through the pelvis. The two *white arrows* in **b** are highlighting the formation of a pararectal abscedation. This patient was treated with the anti-VEGF monoclonal antibody bevacizumab in combination with chemotherapy

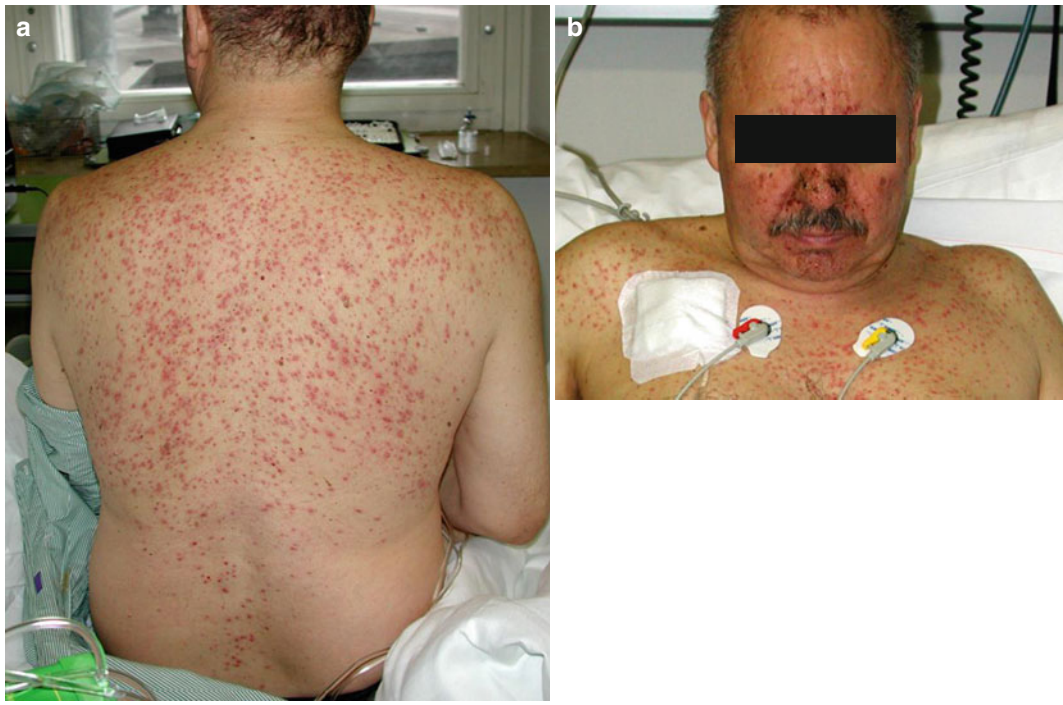

Fig. 5 (**a**, **b**) Patient who developed severe (grade 3 according to CTCAE V4.03) skin rash during weeks 4–6 of chemotherapy combined with the anti-EGFR-directed monoclonal antibody cetuximab

Conclusions

For clinical practice, we have to state that medical anticancer treatment is more demanding than ever, as toxicities are very common, polymorphic and allotropic. They may lead to severe impairment of the patients' safety and quality of life. All members of the treatment team, including the radiologist, need to do their best to support patients during anticancer treatment. Treatment-emergent as well as tumor-related complications may not be missed, and the severity of events must be appropriately classified. In addition, for drug development it has been advocated to move "Toward Patient-Centered Drug Development in Oncology" (Basch 2013).

References

Ando M, Okamoto I, Yamamoto N, Takeda K, Tamura K, Seto T, Ariyoshi Y, Fukuoka M (2006) Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. J Clin Oncol 24(16):2549–2556. doi:10.1200/JCO2005.04.9866

Basch E (2013) Toward patient-centered drug development in oncology. N Engl J Med 369(5):397–400. doi:10.1056/NEJMp1114649

Bronstein Y, Ng CS, Hwu P, Hwu WJ (2011) Radiologic manifestations of immune-related adverse events in patients with metastatic melanoma undergoing anti-CTLA-4 antibody therapy. AJR Am J Roentgenol 197(6):W992–W1000. doi:10.2214/AJR.10.6198

Craig CR, Stitzel CR (2003) Modern pharmacology with clinical applications, 6th edn. Lippincott, Williams & Wilkins, Philadelphia

Duran I, Goebell PJ, Papazisis K, Ravaud A, Weichhart T, Rodriguez-Portal JA, Budde K (2014) Drug-induced pneumonitis in cancer patients treated with mTOR inhibitors: management and insights into possible mechanisms. Expert Opin Drug Saf 13(3):361–372. doi:10.1517/14740338.2014.888056

Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674. doi:10.1016/j.cell.2011.02.013

Heisterkamp N, Stam K, Groffen J, de Klein A, Grosveld G (1985) Structural organization of the bcr gene and its role in the Ph′ translocation. Nature 315(6022):758–761

Klastersky J, Paesmans M (2013) The Multinational Association for Supportive Care in Cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients. Support Care Cancer 21(5):1487–1495. doi:10.1007/s00520-013-1758-y

Monfort JB, Pages C, Schneider P, Neyns B, Comte C, Bagot M, Vignon-Pennamen MD, Viguier M, Lebbe C (2012) Vemurafenib-induced neutrophilic panniculitis. Melanoma Res 22(5):399–401. doi:10.1097/CMR.0b013e3283570792

Niraula S, Seruga B, Ocana A, Shao T, Goldstein R, Tannock IF, Amir E (2012) The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. J Clin Oncol 30(24):3012–3019. doi:10.1200/JCO.2011.40.3824

Phelps MA, Sparreboom A (2014) A snapshot of challenges and solutions in cancer drug development and therapy. Clin Pharmacol Ther 95(4):341–346. doi:10.1038/clpt.2014.15

Seet RC, Rabinstein AA (2012) Clinical features and outcomes of posterior reversible encephalopathy syndrome following bevacizumab treatment. QJM 105(1):69–75. doi:10.1093/qjmed/hcr139

Shinagare AB, Howard SA, Krajewski KM, Zukotynski KA, Jagannathan JP, Ramaiya NH (2012) Pneumatosis intestinalis and bowel perforation associated with molecular targeted therapy: an emerging problem and the role of radiologists in its management. ARJ Am J Roentgenol 199(6):1259–1265. doi:10.2214/AJR.12.8782

Tocchetti CG, Ragone G, Coppola C, Rea D, Piscopo G, Scala S, De Lorenzo C, Iaffaioli RV, Arra C, Maurea N (2012) Detection, monitoring, and management of trastuzumab-induced left ventricular dysfunction: an actual challenge. Eur J Heart Fail 14(2):130–37. doi:10.1093/eurjhf/hfr165

Radiotherapy

T. Bostel and F. Sterzing

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Abstract

The focus of this chapter lies on the description of the general basics of early and late radiation effects and the translation of these pathogenetic processes into imaging; furthermore, a few short clinical examples including imaging patterns of those underlying pathogenetic normal tissue reactions are given to provide a better understanding. In addition, the margin concepts used in radiotherapy as well as the important radiation techniques are summarized, as it is very important for diagnostic radiologists to correlate post-therapeutic tissue and organ changes in follow-up examinations with dose characteristics of a certain treatment to achieve a higher degree of reliability in image interpretation. Furthermore, for

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a better understanding of the cellular basis of the various radiogenic tissue effects, a short refresher about the underlying radiobiological principles is given. The detailed description of specific radiation effects and imaging patterns of clinically relevant organs and tissues, however, follows in the specific organ chapters in order to avoid redundancy.

Abbreviations

CLE	Consequential late effects
COX-2	Cyclooxygenase-2
CT	Computed tomography
CTV	Clinical target volume
3D	Three dimensional
4D	Four dimensional
DNA	Deoxyribonucleic acid
EBRT	External-beam radiation therapy
e.g.	Exempli gratia
GTV	Gross tumor volume
Gy	Gray
i.e.	Id est
IL-1a	Interleukin-1 alpha
iNOS	Inducible nitric oxide synthase
IGRT	Image-guided radiotherapy
IMRT	Intensity-modulated radiation therapy
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NTCP	Normal tissue complication probability
OAR	Organs at risk
PET	Positron emission tomography
PTV	Planning target volume
RBE	Relative biological effectiveness
RR	Relative risk
SBRT	Stereotactic body radiation therapy
TD	Tolerance dose
TGF-ß	Transforming growth factor-ß
TNF-a	Tumor necrosis factor alpha
VOD	Veno-occlusive disease

1 Introduction

Radiotherapy plays a vital role in the oncological treatment concept besides surgical and systemic therapies. Moreover, it is an effective local cancer therapy like surgery, but beyond that it offers the chance for regional high-volume treatments of microscopic tumor deposits or lymphatic pathways as transition to systemic treatments. This pivotal role of radiotherapy is also supported by epidemiological data: More than half of all cancer patients can be cured nowadays, owing to improved efficacy of advanced and mostly multimodal cancer therapies, and around half of these patients receive either radiotherapy alone or radiotherapy in combination with other cancer treatments. Moreover, about two thirds of cancer patients gain valuable palliation by radiation to alleviate the symptoms and to improve the quality of life in the course of their advanced disease.

In recent years, substantial advances in radiological imaging as well as computer hardware and software along with improved design of medical linear accelerators have contributed significantly to the development in radiation therapy. Nowadays, existing modern radiation techniques enable the delivery of conformal dose distributions with steep dose gradients between the tumor and adjacent normal tissue structures. Thus, intensification of the radiation dose to the tumor and reduction of high-dose irradiation of sensitive organs and normal tissues are possible resulting in higher curing rates and lower rates of side effects (i.e., increased therapeutic ratio). However, despite these advances, modern radiotherapy still leaves significant proportions of healthy tissue structures exposed to relatively high doses. This is in part caused by the margin concepts used in radiotherapy. In general, the determination of the planning target volume (PTV) necessarily requires the inclusion of the visible or palpable extent of tumor (i.e., gross tumor volume, GTV) as well as an additional surrounding area without visible branches of the tumor in order to take microscopic disease into account (i.e., clinical target volume, CTV). Furthermore, a patient-specific safety margin is added, if necessary, to account for the range of target motion related to breathing, pulsations, or intestinal peristalsis (e.g., lung or liver lesions) that is often based on four-dimensional (4D) imaging information derived from the planning

CT. And finally, a margin to encompass variability in patient positioning (setup) and mechanical uncertainty is added to create the final PTV. This PTV concept accounts for all available radiation techniques, even though modern approaches such as stereotactic radiation therapy or intensity-modulated radiation therapy enable to adapt the dose distribution more precisely to the tumor boundaries than traditional radiation techniques, which in turn helps to spare the adjacent healthy organs and tissues. On the other hand, PTV can encompass extended areas of normal tissues, dependent on the tumor and disease stage, for example, irradiations of the whole body, whole brain, spinal column, or breast with or without the supraclavicular lymph nodes after breast-conserving surgical treatment.

In the follow-up care of cancer patients, however, it is very important that side effects after therapeutic irradiations are not in general regarded as an indicator for medical malpractice. Moreover, it is an indicator for the best-possible treatment and maximum cure probability when these radiogenic effects manifest with only a defined low incidence of sequelae of defined severity in cured patients (Dorr 2009) (Fig. 1). Regarding the evaluation of side effects, it has also to be mentioned that radiotherapy is increasingly combined with other local and systemic therapeutic approaches such as operation, chemotherapy, or molecular targeting which may lead not only to additive but also to synergistic effects for the tumor response and for organ-specific injuries (Dische et al. 1989; Pedersen et al. 1994). Furthermore, it has to be considered that a certain number of pathological conditions may be triggered by other reasons than specific tumor therapies, such as comorbidities, the tumor itself, or other non-oncological treatments, for example, obstipation due to analgesia with opioids.

As a consequence of increased numbers of cancer survivors and prolongation of survival times, late radiation sequelae as well as secondary cancers are more frequently seen than in the past. This subject has therefore gained more relevance in oncological studies as well as clinical follow-up examinations in recent years. Therefore, it is of utmost importance that radiologists are familiar

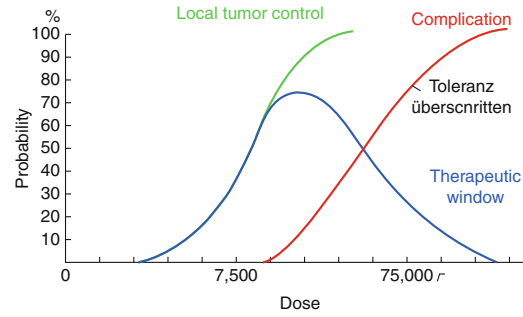

Fig. 1 Dose dependency of tumor control (*green sigmoid curve*) and side effect (*red sigmoid curve*) probability (according to Holthusen): Due to the fact that both curves overlap, there is no chance for complete tumor destruction through radiotherapy without any risk of normal tissue complications – the third *blue curve* depicts the therapeutic window (Figure provided by courtesy of Dr. Dr. Thieke)

with the imaging patterns of these therapy-related tissue reactions as they may both mimic and obscure tumor relapses. Beyond interpretation of posttreatment imaging, diagnostic specialists can make further valuable contributions to increase the therapeutic ratio preceding the radiation treatment process (Terezakis et al. 2011). First of all, every cancer treatment, particularly radiotherapy, heavily relies on accurate staging of the cancerous disease in order to select an appropriate treatment regimen for each patient. It is obvious that misdiagnosis in staging may have fatal consequences for the patient with regard to therapy-associated complications and treatment outcome. For example, unrecognized local tumor extension in an early stage of the disease may result in an insufficient local therapy with persistence of residual tumor cells that trigger the further course of the disease, either with new local symptoms or with propagation of systemic spread of these cells. Similar devastating consequences may result from overtreatment, for example, through radiotherapy, with avoidable early and late therapy effects and worsening of the patient's general condition. This is especially important, since late sequelae of any oncological treatment are therapeutically difficult to influence and characterized by a progressive pattern in many cases (see below). Taken together, accurate staging is an essential precondition for a successful treatment

of cancer patients. Further input of diagnostic specialists may be provided during the routine radiation oncology workflow: Delineation of the macroscopic tumor (GTV) often requires additional advanced imaging modalities such as MRI or PET/CT and reaches beyond the normal anatomic information. As tumor imaging has been increasing in both the amount and the complexity of information, an in-depth knowledge of oncologic radiology has become more and more crucial in recent times. Furthermore, tumor tissue is often difficult to distinguish from normal tissue changes, for example, due to prior treatments or stromal reactions seen in infiltrating cancers, radiologic input may add to the precision in delineating the GTV. In summary, radiation therapy has become increasingly based on multimodal imaging, and oncologically trained diagnostic radiologists are increasingly important for the successful application of modern radiotherapy treatments (Terezakis et al. 2011).

2 Radiation Delivery Techniques

For radiologists it is important to consider not only the delivered overall dose for image interpretation of normal tissue changes but also the used treatment technique. This means that depending on the irradiation technique, a given specific overall dose may be distributed in normal tissues in completely different ways, and thus the organ exposure can vary significantly with consecutive different image presentations in the follow-up. Furthermore, it would be extremely helpful for radiologists if dose overlays from treatment planning software could be integrated into PACS workstations in the near future to achieve a higher degree of safety in image interpretation.

2.1 Traditional External-Beam Radiation Therapy (EBRT)

First, therapeutic applications of ionizing radiation started early after their discovery by Conrad Roentgen in 1895. For many decades, irradiation of cancerous tissues was performed with X-ray devices, which allowed only relatively low energy doses with peak doses near the entrance site of the beam. Thus, major drawbacks were dose-limiting radiation effects in skin and epidermis and the rapid decline of the depth-dose curve being unfavorable especially for the treatment of deep-seated local tumors.

It was only in the 1950s until high-energy linear accelerators were developed – a milestone for the specialty of radiation oncology. From the 1950s to the 1980s, radiation treatment was administered by the use of planar radiographs in two dimensions, which visualized osseous landmarks. These bony landmarks were used for delineation of radiation portals and localization of therapeutic targets. Depending on the tumor site, the number of beams used for radiotherapy ranged from two to six. However, treatment planning was limited by poor tumor visualization of mainly X-ray-based imaging methods and techniques available for radiation delivery (Purdy 2008; Bortfeld and Jeraj 2011).

2.2 Conformal Radiation Therapy

In the 1980s, cross-sectional imaging procedures (i.e., CT and MRI) entered clinical routine, which were essential for a more accurate delineation of cancerous tissues and risk structures. These advances in radiological imaging were fundamental for further progress in radiation oncology with development of computerized treatment planning and delivery systems that enabled an exquisite tailoring of 3D radiation dose distributions to the cancerous tissues (Bortfeld and Jeraj 2011). These 3D conformal dose applications were reached by the use of a larger number of lower-dose radiation beams aimed at the target volume from different directions (up to 10 beams) (Fig. 2). As a consequence, the low-dose exposition of healthy tissues was increased, but the amount of tissues receiving high doses was significantly decreased (Bortfeld and Jeraj 2011); thus, the dose in the tumor could be escalated, while the surrounding healthy tissues and organs at risk could be protected better than with traditional EBRT helping to increase the therapeutic ratio. Furthermore, dynamic multileaf collimators were developed and clinically established for more

precise shaping of radiation beams compared to the previously used lead blocks (Purdy 2008).

Modern conformal radiation therapy plans may also include intensity-modulated radiation therapy (i.e., IMRT) and stereotactic body radiation therapy (i.e., SBRT), which are described in the next two sections.

2.3 Intensity-Modulated Radiation Therapy (IMRT)

The mathematical basis of IMRT was developed in the early 1980s to address the problem of irradiation of complex-shaped tumors in close proximity to or within risk structures, for example, paraspinal tumors (Fig. 3). But it still took a while until theoretical knowledge was put into practice, with first IMRT treatments applied to patients in 1997. The concept of IMRT is based on two decisive pillars, which are inverse treatment planning and nonuniform photon intensities across each of several radiation beams – usually 5–9 in modern treatment plans (Brahme et al. 1982). In the pre-IMRT era, physical dose distribution was calculated by trial and error; this means by trying out different intensities and directions of radiation beams. IMRT, on the other hand, takes the abovementioned path of inverse treatment planning, that is, dose distribution is tailored exactly to the target volume at the beginning of the planning process. Subsequent modeling of the direction, contour, and intensity of each treatment beam follows this by computerized treatment planning systems. For this purpose, radiation beams are subdivided into many segments and subsegments (i.e., often more than 100), in which intensities can be specified independently of each other by the use of multiple overlapping field segments or moving collimator leaves. This enables reduction of the dose for a certain beam direction, if risk structures are included in the beam. However, this approach would result in underdosing of the target volume, if conventional radiation techniques were used (Fig. 4). In IMRT plans, the lack of dose in the target volume is compensated by additional dose through another beam (Sterzing et al. 2009; Paumier et al. 2011).

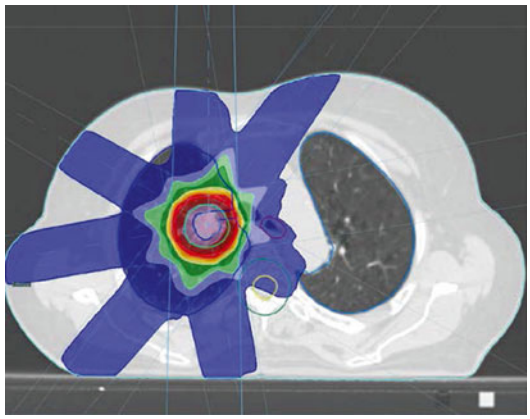

Fig. 2 Dose distribution for primary irradiation of an NSCLC in the right upper lobe. The *purple-* and *red-colored* inner region represents the high-dose region. The *yellow*, *green*, and *blue* areas represent decreasing isodose lines towards the periphery

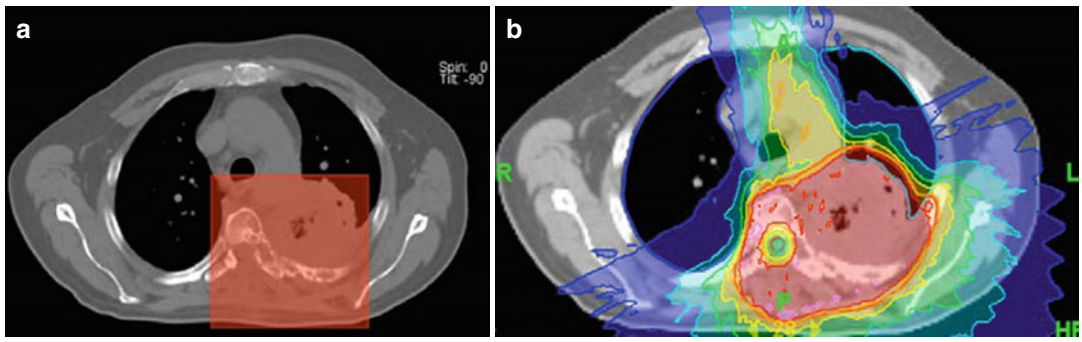

Fig. 3 Presentation of a mass along the dorso-cranial thoracic wall left sided with infiltration of the paravertebral space, upper part of the thoracic spine and spinal canal in the planning CT (status post-laminectomy) (**a**). In IMRT plan (**b**) with depiction of steep dose gradients to the surrounding normal tissues and the **myelon** (*red* area represent high-dose area; *yellow*, *green*, and *blue* areas represent decreasing isodoses)

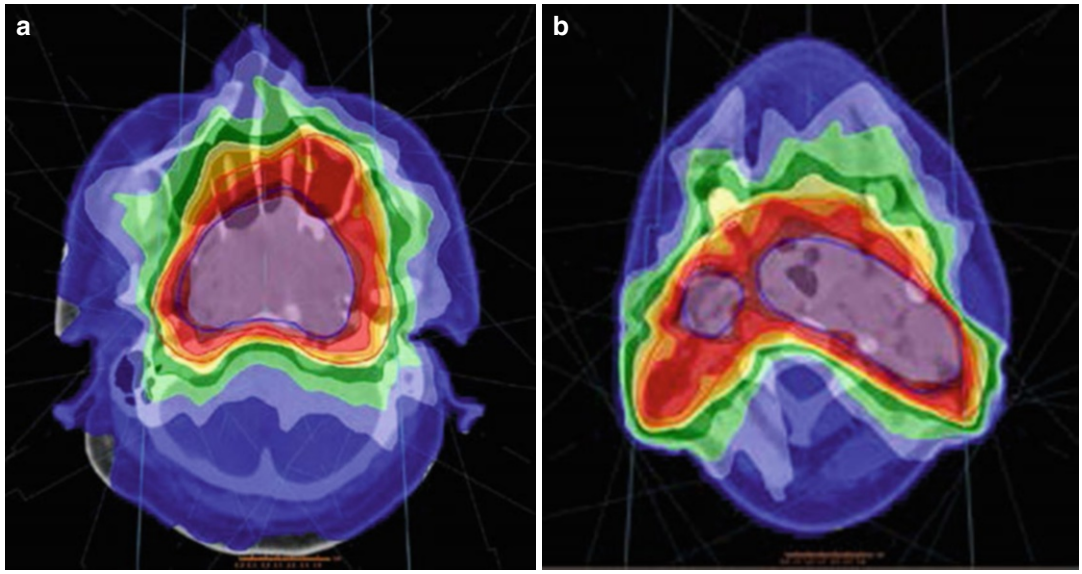

Fig. 4 IMRT plan with 9 beams for irradiation of an advanced nasopharyngeal cancer with infiltration of the skull – note the *purple area* of dose distribution, which indicates the high-dose region encompassing the primary tumor and the steep dose gradients, which enables an excellent sparing of the adjacent brain stem (**a**). Same patient showing the integrated boost concept, that is, the primary tumor and lymph node metastases receive the boost (*purple-colored area*) and the cervical lymphatic pathways a slightly lower dose (*red-colored area*) to treat potential microscopic tumor deposits (**b**). The *yellow*, *green* and *blue* coloured areas indicate the decreasing isodoses towards the periphery

Taken together, accurate computation of an optimized dose distribution in IMRT makes it possible to apply a highly conformal radiation dose to tumors of complex shapes in the immediate vicinity of high-risk organs such as the optic nerve, the brain stem or spinal cord, the intestine, or the lungs without damaging healthy surrounding tissues. This implies that the high-dose region is smaller and the low-dose region is larger at IMRT than at 3D conformal radiation therapy (Purdy 2008; Paumier et al. 2011). However, the highly conformal nature of IMRT makes it more sensitive to geometric error, which was the rationale for development of image-guided radiation therapy (i.e., IGRT) techniques in order to ensure that radiation dose is delivered as planned (Perks et al. 2008; Boda-Heggemann et al. 2011; Sterzing et al. 2011).

2.4 Stereotactic Body Radiation Therapy (SBRT)

SBRT was pioneered in the 1980s and represents a special form of 3D conformal radiotherapy, which enables precise delivery of large single doses (in general, more than 3 Gy) in one or a just a few fractions to a confined area. Compared with other conformal radiation techniques, the advantage of SBRT lies mainly in maximization of tumor cell killing while minimizing the dose to the surrounding normal tissues (Kavanagh et al. 2011). Another advantage is shortening of the overall treatment time, which is more convenient for the patients.

However, safety and efficiency of this approach strongly depend on several factors such as adequate and very often multimodal treatment planning, accurate dose delivery, rigid immobilization, and/or regular image-guidance and dynamic-motion compensation methods.

The use of highly dose-intense or ablative treatment regimens imposes tough requirements on target delineation and definition of organs/structures at risk; thus, besides planning CT other imaging modalities like MRI or PET/CT are very often included into the planning process. Highly conformal dose distributions are achieved by the use of a large number of beams from various directions which are usually more narrowly