Tumor Biology's Impact on Clinical Cure Rates

19

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CONTENTS

KEY POINTS

- While tumor grading might influence, for example, the need for postoperative radiotherapy, current data do not suggest a clear impact on local tumor control probability.
- Local tumor control probability decreases with increasing tumor volume, which is caused by the increase of the number of cancer stem cells with tumor volume.
- Other stem-cell-related parameters, such as cancer stem-cell density or intrinsic radiosensitivity, are currently not known for individual tumors; thus, predictive assays that could tailor the prescribed dose to the individual patient are not yet a clinical tool.
- Repair capacity substantially impacts radiosensitivity. As this parameter can also substantially vary within one tumor entity, research into predictive assays for repair capacity of individual tumors may contribute to further improvement of tumor control rates.
- Repopulation of cancer stem cells during fractionated radiotherapy is among the most important mechanisms of radioresistance of tumors.
- In addition to the intertumoral heterogeneity, strong evidence has accumulated that parameters of the tumor micromilieu that affect radiosensitivity may also be heterogeneously distributed within the individual tumor (intratumoral heterogeneity).

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19.1 Introduction

Cure of cancer is defined as locoregional tumor control without distant metastases and without life-threatening treatment complications. Radiotherapy is one of the main cancer treatment modalities. As a local treatment, its aim is to achieve locoregional tumor control by inactivation of all cancer stem cells within the primary tumor and regional lymph nodes. Treatment effects on local tumor control are therefore the focus of this chapter; however, also potential indirect effects on the risk of distant metastases are briefly considered.

It is well recognized that the probability to permanently control tumors increases as a sigmoid function with increasing radiation dose. Below a threshold, the dose is not sufficient to inactivate all cancer stem cells in a tumor, i.e. all tumors recur. After this threshold, tumor control increases with increasing radiation dose, approaching 100% at high doses.

Even if some data suggest a higher metastatic potential of tumors during radiotherapy, successful radiotherapy is an effective way to stop metastasis at the source, thereby importantly contributing to overall survival of the patient.

Inclusion of biological parameters of the individual tumors is anticipated to further improve the results of radiotherapy by tailoring dose and treatment schedule, by combining radiotherapy with modern drugs, and by taking into account intratumoral heterogeneity based on biological imaging.

19.2 Inactivation of Cancer Stem Cells and Local Tumor Control

A cancer stem cell is defined as a cell within a tumor that possesses the capacity to self renew and to generate the heterogeneous lineages of cancer cells that comprise the tumor (Clarke et al. 2006). In the context of radiotherapy a cancer stem cell is defined as a cell that, if not killed by radiation, forms a tumor recurrence (Baumann et al. 2008, in press). Curative radiotherapy therefore aims at inactivation of all cancer stem cells in the primary tumor and locoregional lymph nodes. It is well recognized that the probability to permanently control tumors (tumor control probability, TCP) increases as a sigmoid function with increasing radiation dose. Below a threshold, the dose is never sufficient to inactivate all cancer stem cells in a tumor, i.e. all tumors recur. After this threshold, tumor control increases relatively steeply with increasing radiation dose, approaching 100% at high doses. From the dose–response curves descriptors of their relative position, such as the radiation dose necessary to control 50% of the tumors (tumor control dose 50%, TCD50), can be easily derived. The sigmoid shape of the dose–response relationship for local control reflects the exponential inactivation of cancer stem cells by radiation and a Poisson distribution of surviving cancer stem cells (Munro and Gilbert 1961; Suit et al. 1987; Bentzen and Tucker 1997; Bentzen 2002; Baumann and Petersen 2005; Baumann et al. 2005).

For determination of the outcome of preclinical as well as clinical studies on radiation, it is important to discriminate local tumor control from volume-dependent endpoints such as tumor regression or tumor growth delay. Those cells which may form a recurrence after therapy, i.e. cancer stem cells, constitute only a small proportion of all cancer cells, whereas the bulk of tumor cells are non-tumorigenic (Baumann et al. 2008, in press); thus, changes in tumor volume after therapy are governed by the bulk of tumor cells, i.e. primarily by the non-stem cells. As outlined above, local tumor control is dependent on the complete inactivation of the subpopulation of cancer stem cells (Baumann et al. 2008). For a variety of reasons, including time and cost, volume-dependent endpoints are currently widely used for preclinical studies in cancer research. This carries a substantial risk that new treatments may be optimized for their effect on the bulk of non-stem cancer cells, with no improvement in the curative potential (Baumann et al. 2008). This has been demonstrated in several experiments which showed effects of novel combined radiation treatments on growth delay, but for the same treatment, not on the local tumor control (reviewed in Krause et al. 2006; Baumann et al. 2008). Overall, these experiments support the use of cancer-stem-cell-specific endpoints to test the effect of new treatment schedules or the predictive value of biological parameters in preclinical and clinical radiation oncology.

19.3 Heterogeneity Between Tumors and Steepness of Dose–Response Curves

A widely used method to quantify the steepness of dose–response relationships for local tumor control is the normalized dose–response gradient, or γ value (Brahme 1984; Bentzen and Tucker 1997). This value defines the percentage of increase in response for a 1% increase in dose at a specified response level in the

steep part of the dose–response curve, e.g. 50% (γ50). It is important to note that dose–response curves for tumor control in experiments, and particularly in the clinical setting, are usually shallower than those calculated using biostatistical modelling. This is caused by heterogeneity in biological characteristics of the tumors. Figure 19.1 shows as an example the results of an experiment on nine different human head and neck squamous cell carcinomas (SCC) in nude mice. All tumors were irradiated at the same size with an identical fractionation schedule, i.e. 30 fractions within 6 weeks. Despite that all tumors are of the same entity, the dose relationships differ substantially in position and steepness. Four tumor lines are relatively sensitive with TCD50 values of 40–50 Gy. Two tumor lines exhibit intermediate resistance, whereas three lines, with TCD50 values of 90–130 Gy, are exquisitely radioresistant. The bold curve represents the composite dose–response relationship of all nine tumor lines. It is considerably less steep than most of the underlying dose–response relationships of the individual tumor models. The composite dose–response curve is close to the current clinical situation if strictly size-matched tumors of the same histology and origin (e.g. head and neck SCC) in different patients are evaluated. The reason for the relatively flat composite dose–response curve is that biological characteristics important for local tumor control, e.g. cancer-stem-cell, density or intrinsic radiosensitivity, are currently not known for the individual tumor. If we knew the biological parameters, which impact the dose–response for individual tumors from predictive assays, with sufficient certainty, we could tailor the prescribed dose to the individual patient. For example, if we knew that a tumor in a given patient falls under the four sensitive tumor lines shown in Fig. 19.1, we could limit the radiation dose without jeopardizing local tumor control, thereby sparing normal tissues. If, in contrast, a given tumor falls under the three resistant lines, one would need to consider dose escalation, combination with radiosensitizing drugs, combination with surgery or LET beams if we want to achieve local control. The current status of determination of biological parameters to predict local tumor control is discussed in Sect. 19.5.

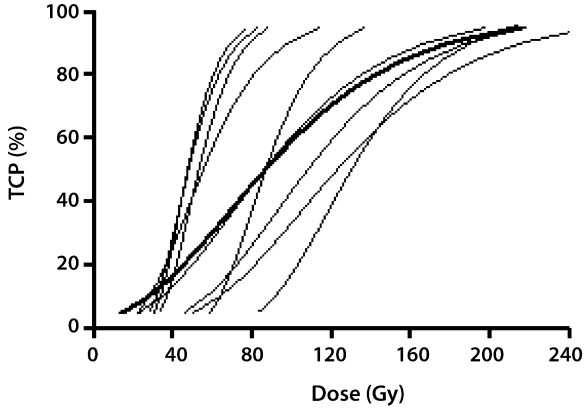

Fig. 19.1. Impact of heterogeneity in biological characteristics of tumors on dose–response for local tumor control probability (TCP). Nine different human head and neck squamous cell carcinomas in nude mice were irradiated at the same size with 30 fractions in 6 weeks. Despite that all tumors are of the same entity, the dose relationships differ substantially in position and steepness. The *bold curve* represents the composite dose–response relationship of all nine tumor lines

19.4 Heterogeneity Within Individual Tumors and Its Potential Importance for Optimizing Radiation Dose Distributions

In addition to differences of the overall radiosensitivity between different tumors (intertumoral heterogeneity), strong evidence has accumulated that biological parameters which affect radiosensitivity may also be heterogeneously distributed within the individual tumor (intratumoral heterogeneity). Figure 19.2 shows examples of heterogenous distribution of hypoxic tumor volumes detected by functional histology using the hypoxia marker pimonidazole (Fig. 19.2a) or by autoradiography using the hypoxia-specific tracer 18F-misonidazole (Fig. 19.2b) in an experimental SCC. Such intratumoral heterogeneity can also be detected by histology or functional imaging in patients. As an example, Fig. 19.2c shows a PET-CT after injection of 18-Fluordeoxyglucose or 18-F-misonidazole in a patient suffering from head and neck SCC. Knowledge of the spatial distribution of radioresistant vs radiosensitive tumor subvolumes, in principle, may be the basis for individualized, biologically adapted heterogeneous radiation dose distribution ("dose painting") to improve local tumor control (Ling et al. 2000; Bentzen 2005; Baumann 2006). Of interest in this context are recent reports that cancer stem cells may not be generally distributed evenly over the tumor but may accumulate preferentially in so-called microenvironmental niches (Gilbertson and Rich 2007). These niches cannot yet be detected by imaging methods; however, it appears promising to explore the possibility of development of stem-cell-specific imaging modalities for development of irradiation techniques that allow inhomogeneous dose distributions adapted to both, inhomogeneous stem-cell density and inho-

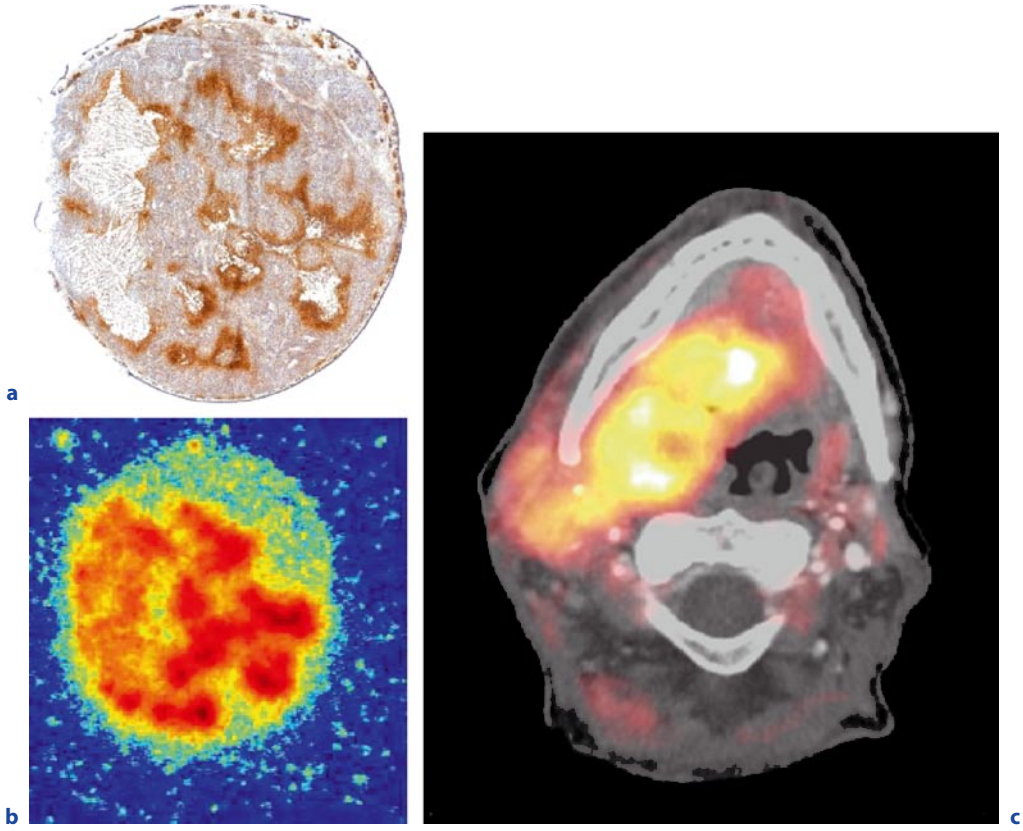

Fig. 19.2a–c. Heterogenous distribution of hypoxic tumor subvolumes detected by functional histology (pimonidazole; **a**) or by autoradiography (18F-misonidazole; **b**) in an experimental squamous cell carcinoma. Similar heterogeneity is regularly observed in patient tumors. **c** Heterogeneous distribution of the PET hypoxia marker 18F-misonidazole in comparison with the CT volume of the tumor

mogeneous distribution of microenvironment-driven radiosensitive and radioresistant tumor subvolumes.

19.5 Important Biological Parameters that Impact Local Tumor Control

19.5.1 Histology and Grading

It is well recognized that tumors of different histology, e.g. seminoma vs glioblastoma, are characterized by different radiosensitivity. Because of its strong predictive power, categorization of tumors by histology has been a major basis for dose prescription for already a century now (Beck-Bornholdt 1993). For a given histology, the importance of grading for local tumor control is more complex to judge. Poor differentiation has generally been associated with poor prognosis, but this appears more related to stage at diagnosis and to the rate of metastases than to the chance to locally control the tumor by radiation. Local subclinical extension of tumors is generally less in well-differentiated tumors than in poorly differentiated or undifferentiated tumors; therefore, grading is an important parameter to prescribe postoperative radiotherapy and to design margins in several tumor entities, e.g. soft tissue sarcoma, glioma, head and neck and endometrial carcinoma. The impact of grading on radiosensitivity of size-matched tumors of the same entity is less clear. It is often suspected that well-differentiated tumors are more radioresistant than undifferentiated tumors of the same histology (Bergonie and Tribondeau 1959). While such a correlation has been observed in some clinical series, it is overall not well supported by clinical outcome data (Stuschke et al. 1993). As others before (Fletcher 1980, 1988), the authors of the present chapter suspect that the idea that well-differentiated tumors are radioresistant, historically originates from the experiments performed by Bergonie and Tribondeau on rat testis.

These experiments showed that irradiation destroyed germinal cells, whereas the interstitial tissue and sertoli syncytium remained unimpaired. They concluded that irradiation is more effective in cells that have a greater reproductive activity (Bergonie and Tribondeau 1959). Experimental investigations in vitro revealed that the dose necessary to eradicate tumor cell spheroids was higher in undifferentiated than in differentiated tumor lines, whereas the capacity to recover from sublethal radiation damage during fractionated irradiation was higher in better differentiated tumor lines (Stuschke et al. 1993). Another factor that may have contributed to the idea of radioresistance of well-differentiated tumors is that there is a correlation between speed of tumor growth and velocity of tumor regression (Fletcher 1980, 1988). This may lead to faster tumor regression in undifferentiated tumors and to the impression of higher radiosensitivity, which may vanish when permanent local tumor control is investigated; however, there is some suggestion that, as a reminder of their epithelial tissue of origin, well-differentiated head and neck SCCs may have a higher capacity for repopulation of cancer stem cells as a consequence of radiation injury (see Chap. 15). This would indeed lead to higher radioresistance of such tumors, but only after long fractionation schedules and not after accelerated treatments or single-dose stereotactic irradiation. In contrast, in prostate cancer, based on the results of randomized trials, higher doses are applied for intermediate-risk tumors than for low-risk tumors. Gleason score, as a measure of differentiation, is one of the parameters that determines the risk category (Jereczek-Fossa and Orecchia 2007). Overall, no general conclusion can currently be drawn regarding the impact of grading on local tumor control probability after radiotherapy. The often-heard statement that, based on examination of histological specimens, a tumor, because of good differentiation, would not be radiosensitive, should not be accepted by today's radiation oncologists. Better biological parameters for prediction are urgently needed.

19.5.2 Tumor Volume

It is the general experience of radiation oncologists that large tumors are more difficult to control by radiotherapy than small tumors. On the one hand, this is due to the often very large volumes of normal tissues irradiated to high doses, which can be dose- (and therefore success-) limiting in large tumors. On the other hand, the number of cancer stem cells increases with increasing tumor volume, leading to a higher radiation dose necessary for local tumor control (see sect. 19.2). A strong correlation between tumor control dose and the logarithm of tumor volume has been demonstrated in experimental tumor models as well as in clinical studies (Baumann et al. 1990a; Johnson et al. 1995; Bentzen and Thames 1996; Dubben et al. 1998). Exactly this correlation is predicted by an expected linear increase of the number of cancer stem cells with tumor volume and radiobiological models of stem-cell inactivation (Suit et al. 1965; Baumann et al. 1990a; Johnson et al. 1995; Bentzen and Thames 1996; Kummermehr and Trott 1997; Dubben et al. 1998).

19.5.3 Stem-Cell Density

It has been demonstrated in preclinical experiments that the number of cancer cells which need to be transplanted to achieve a tumor take in half of the recipient animals (tumor dose 50%, TD50) may vary by several logarithms between different tumor models (Hill and Milas 1989). The TD50 is a direct measure of stem-cell density in a given tumor (Hill and Milas 1989; Baumann et al. 1990a, in press). Experiments which show that the TCD50 after single doses correlates with the logarithm of TD50, implying that a higher stem-cell content per volume tumor leads to a higher radioresistance, are of great importance (Hill and Milas 1989). Recently published data on experimental SCC extend these studies and show a significant correlation of TCD50 after single doses with TCD50 after irradiation with 30 fractions over 6 weeks. These data suggest that pretreatment tumor stem-cell density and cellular radiosensitivity are major predictors of local control after clinically relevant radiation treatment.

19.5.4 Intrinsic Radiosensitivity

The above-mentioned experiments showing that TCD50 after fractionated irradiation correlates closely with TCD50 after single doses indicate that the number of cancer stem cells to be inactivated and their intrinsic radiosensitivity are major determinants of radioresistance of a given tumor. This is further supported by other experiments, which showed that only the combination of stem-cell density determined by TD50 and their intrinsic radiosensitivity significantly predict tumor radiocurability (Gerweck et al. 1994). Intrinsic radiosensitivity has widely been described by the SF2, i.e. the surviving fraction of tumor cells in vitro after

irradiation with 2 Gy, a dose often used in the clinic. SF2 measures clonogenic survival, defined as colony formation under idealized growth conditions in vitro. It is noteworthy that the five to six cell divisions necessary for colony formation (usually defined as >50 cells) do not necessarily measure cancer stem cells, as these are defined as being able to form a complete tumor (see above). Re-evaluation of SF2 values for different tumor cell lines has shown that those histologies, which are expected to be radioresistant in the clinic, have, on average, higher SF2 values compared with more radiosensitive tumors (Malaise et al. 1986). Correlation of SF2 with survival or local tumor control in individual patients in some cases supported the importance of intrinsic radiosensitivity of clonogenic tumor cells for outcome of radiotherapy (Ramsay et al. 1992; Girinsky et al. 1994; West et al. 1997); however, numerous other data sets did not confirm such a correlation (Brock et al. 1990; Allalunis-Turner et al. 1992; Taghian et al. 1993; Eschwege et al. 1997; Stausbol-Gron and Overgaard 1999). Underlying reasons for these contradictory results include most likely that current clonogenic ex-vivo assays do not necessarily measure the radiosensitivity of cancer stem cells or yield different results because of differences between in-vivo and in-vitro microenvironmental conditions, including differences in cell–cell and cell–stroma interactions.

19.5.5 Apoptosis vs Other Cell-Death Mechanisms

Cells can die in several ways (Okada and Mak 2004; Brown and Attardi 2005), i.e. by apoptosis, mitotic catastrophe, senescence, necrosis and autophagy. Mitotic catastrophe caused by lethal chromosome damage is the most important cell-death mechanism for the effect of radiotherapy of solid tumors. After irradiation, cells can pass through few mitotic cycles before mis-segregation of chromosomes or cell fusion leads to the loss of the replicative potential of cells. While apoptosis has obtained much interest as a cell-death mechanism in neoplastic disease, it appears not to be the main mechanism of radiation-induced cell death, at least not in solid tumors. Apoptotic index or levels of proteins involved in apoptosis (e.g. p53, Bcl-2) are not predictive of the response of solid tumors to radiotherapy (Brown and Wouters 1999; Brown and Wilson 2003; Brown and Attardi 2005). For example, the significantly decreased apoptotic fraction in Bcl-2 overexpressing cells after irradiation did not change clonogenic cell survival (Wouters et al. 1999). Thus far, no distinct radiation-dependent pathway for cellular necrosis has been described; however, it is has been shown in a variety of studies that tumors after radiotherapy or radiochemotherapy often show massive necrosis, which sometimes correlates with improved prognosis (Thomas et al. 1999; Vecchio et al. 2005; Dincbas et al. 2005). It can be speculated that this radiation-induced necrosis is the consequence of cell death by mitotic catastrophe in combination with effects of irradiation on the tumor microenvironment.

19.5.6 Repair Capacity and Fractionation Sensitivity

Both, tumors and normal tissues, repair the vast majority of radiation-induced DNA damage within hours after induction. Remaining, i.e. non- or falsely repaired, double-strand breaks are presently considered to be the most important mechanism for radiation-induced cell kill (Frankenberg-Schwager 1989; Iliakis 1991; Dikomey et al. 2003; Kasten-Pisula et al. 2005). Radiosensitivity of individual tumors might be predictable by evaluation of DNA repair-related proteins. Currently among the best investigated proteins is phosphorylated histone H2AX (γH2AX). Phosphorylation of H2AX occurs in response to DNA double-strand breaks, e.g. induced by irradiation. Foci formation of γH2AX around the double-strand breaks can be visualized microscopically after antibody labelling and correlates with the repair kinetics of DNA double-strand breaks. Recent preclinical data suggest a predictive value of residual γH2AX foci measured 24 h after irradiation with the individual radiosensitivity (Klokov et al. 2006) as well as a correlation with tumor hypoxia (Bristow et al. 2007). The capacity to repair sublethal damage between irradiation fractions can be expressed by the α/β value of different tumors. Generally, α/β values of many tumors are in the range of early-responding normal tissues or higher (Williams et al. 1985), whereas late-responding normal tissues usually have low α/β values, i.e. a better repair capacity (van der Kogel 2002). This differential has been the basis for successful clinical introduction of hyperfractionated irradiation schedules, particularly in head and neck SCC (Bourhis et al. 2006); however, there are important exceptions, and some tumor entities appear to be characterized by significantly low α/β values in the range of late-responding normal tissues or even lower. Thus far, this has been clinically best investigated for breast cancer by several randomized clinical trials; however, also for prostate cancer, low-grade soft tissue sarcoma, melanoma and possibly other tumors low α/β values are suspected from clinical data (Thames and Suit 1986; Brenner and Hall 1999; Stuschke and

Thames 1999; Williams et al. 2007; Bentzen et al. 2008a,b). For tumors with lower α/β values compared with the surrounding normal tissues, hypofractionation may be a viable option to improve the therapeutic ratio of radiotherapy, particularly as hypofractionation may also be a convenient way to accelerate the treatment, thereby counteracting repopulation (see below). Adaptation of the dose per fraction currently is limited to tumor entities and cannot be tailored to tumors in individual patients. As it is known that the repair capacity can also substantially vary within one tumor entity (Williams et al. 1985; Petersen et al. 1998), research into predictive assays for repair capacity of individual tumors may contribute to further improvement of tumor control rates.

19.5.7 Repopulation

Repopulation of cancer stem cells during fractionated radiotherapy is among the most important mechanisms of radioresistance of tumors. Repopulation has been best demonstrated for head and neck SCC where a host of preclinical and randomized clinical studies are available. Repopulation is extensively reviewed in Chap. 15. Because of its importance, and the recognized heterogeneity between different tumors (Petersen et al. 2001; Hessel et al. 2004a,b), intense efforts have been made to develop predictive assays for repopulation, which may be used to select patients for accelerated fractionation schedules. While initial studies on the potential doubling time of tumor cells, studied by flow cytometry after BrdU or IrdU labelling, showed promise, a large multicentre study did not reveal a predictive value for local tumor control or survival after radiotherapy (Begg et al. 1999). As outlined above, several studies in head and neck SCC suggest more pronounced repopulation in better-differentiated tumors. Also expression of the epidermal growth factor receptor (EGFR) might correlate with repopulation of cancer stem cells (Schmidt-Ullrich et al. 1997; Petersen et al. 2003; Eriksen et al. 2004a,b, 2005a,b; Bentzen et al. 2005; Krause et al. 2005; Baumann et al. 2007). In addition, TP53 mutations might predict local tumor control after accelerated radiotherapy in head and neck cancer (Alsner et al. 2001; Eriksen et al. 2005). As a large number of factors are involved in response of tumors to radiotherapy, it is likely that multiparametric approaches will better predict response to specific treatment schedules. While several studies were published on prognostic implications of molecular marker profiles (e.g. van't Veer et al. 2002; Seigneuric et al. 2007), studies on the predictive value for radiotherapy are limited thus far; however, using the candidate-gene approach, which concentrates on genes or proteins that are known to be involved in tumor (or normal tissue) response, promising results for potential prediction of the response to accelerated radiotherapy schedules could be shown in two studies (Buffa et al. 2004; Eriksen et al. 2004).

19.5.8 Hypoxia and Other Factors of the Tumor Micromilieu

The chaotic vasculature of malignant tumors causes a heterogeneous oxygenation with well-oxygenated areas, hypoxic vital tumor regions and necrotic areas (Vaupel et al. 1989; Vaupel 2004). As hypoxic cancer stem cells are known to be more radioresistant, a number of studies tested the predictive value of tumor oxygenation on local tumor control after radiotherapy. Using polagraphic needle electrodes to measure pO2, the *prognostic* value of tumor hypoxia on local tumor control, and also on distant metastases, has been demonstrated for different tumor entities (Hockel and Vaupel 2001). In the largest study performed to date, a multicentric analysis of almost 400 patients with head and neck carcinoma, better oxygenation was prognostic for survival (Nordsmark et al. 2005). Preclinical data show that tumor hypoxia measured in histological sections of untreated tumors after injection of the hypoxia marker pimonidazole significantly correlates with local tumor control after fractionated irradiation (Yaromina et al. 2006). Also analysis of 43 tumors from head and neck cancer patients treated in a phase-II clinical trial indicates a correlation of pretherapeutic pimonidazole hypoxic fraction with local tumor control as well as with overall survival (Kaanders et al. 2002). In preclinical investigations plasminogen activator inhibitor-1 in tumor tissue correlated with hypoxia and tumor control after fractionated irradiation. Retrospective evaluation of plasma osteopontin levels, a protein which is activated by hypoxia, for head and neck cancer patients treated in the randomized DAHANCA 5 trial, showed a significant correlation with locoregional tumor control and disease-specific survival after radiotherapy (Overgaard et al. 2005). Furthermore, the outcome of patients with high, but not with low, osteopontin levels could be improved by the hypoxic cell sensitizer nimorazole, suggesting not only a prognostic but also a predictive value of osteopontin (Overgaard et al. 2005). It is still unclear which hypoxia marker has the highest relevance as a possible predictor for the outcome of radiotherapy (Nordsmark et al. 2007). Early

experience is accumulating showing that hypoxia measured by PET imaging may yield predictive information useful for radiotherapy treatment planning and monitoring (Thorwarth and Alber 2008). Independent of hypoxia, high tumor lactate levels have been shown to correlate with high TCD50 values after fractionated radiation in a preclinical study (Quennet et al. 2006) and with prognosis in clinical investigations (Walenta et al. 2000). As lactate levels can be mapped using specialized MRI, these results bear considerable promise for further studies assessing this technology for radiotherapy treatment planning.

19.6 Local Control and Distant Metastases

It has been speculated that cancer, at some very early stages, almost always reflects systemic disease. In addition, it has been hypothesized that those tumors which are radioresistant, and can currently not be locally controlled by radiation, are particularly malignant and therefore have a very high risk of subclinical distant metastases. Also, some experiments seem to suggest that radiation itself might increase the risk of tumors to metastasize (Baumann et al. 1990b; O'Reilly et al. 1994; Camphausen et al. 2001). These three arguments seem to support the conclusion that improvement of local tumor control by more effective radiation treatments will have only negligible or no impact on survival. Nevertheless, there is ample experimental and clinical evidence that improved local tumor control improves survival. Several experiments demonstrate that the incidence of distant metastases in the same murine tumor lines is higher for local recurrences than in locally controlled tumors after radiotherapy or surgery (Table 19.1). The most likely explanation for this finding is that the overall integral tumor burden is higher in local recurrences. Even if the risk of a cancer cell to form a metastasis might be increased during radiation, e.g. because of altered gene expression or because of disturbance of tumor cell (stromal interactions), the overall number of tumor cells at risk decreases very rapidly during radiotherapy, which leads to a significant overall decrease in the risk to metastasize per tumor (Ramsay et al. 1988; Baumann et al. 1990a,b). The observation of less-distant metastases in locally controlled tumors has been confirmed in extensive retrospective analysis of clinical results (Suit et al. 1970; Suit and Westgate 1986; Suit 1992). Correlation analysis of radiosensitivity and metastasis has revealed that the cellular radiosensitivity measured ex vivo in head and neck, cervix or endometrial cancer was not different for patients with or without distant metastases. Furthermore, no correlation was found between TCD50 and incidence of distant metastases in a panel of 24 murine tumor models (Suit et al. 1994). Last but not least, a number of randomized trials published in the past two decades clearly demonstrate that improved local control of, for example, breast can-

Table 19.1. Local tumor control and metastatic spread (murine tumors). *SCC* squamous cell carcinoma, *RT* radiotherapy, *OP* surgery

Reference	Tumor	Treatment	Lung metastases	
			Controlled (%)	Relapsed (%)
Sheldon et al. (1974)	Mammary carcinoma	RT	8	35
Todoroki and Suit (1985)	Sarcoma	OP	7	26
		RT	9	56
		OP + RT	7	45
Ramsay et al. (1988)	SCC	RT	7	43
		RT	3	13
Baumann et al. (1990b)	SCC	RT	5	25
		RT	10	40

cer, rectal carcinoma, head and neck carcinoma, lung cancer, or cancer of the uterine cervix after intensified locoregional treatment approaches lead to better survival or decreased rates of distant metastases (Horiot et al. 1992; Gunderson and Martenson 1993; SRC Group 1997; Whelan et al. 2000; Bourhis et al. 2004); therefore, the overall conclusion of this chapter is that successful radiotherapy is an effective way to stop metastasis at their source, thereby significantly contributing to overall survival of the patient.

19.7 Conclusion

Several tumor biological parameters have been identified to impact local tumor control after radiotherapy in preclinical models as well as in clinical tumors. Some of these parameters are presently regularly considered for prescription of treatment in clinical practice, whereas for several other parameters predictive assays are still evolving. Inclusion of biological parameters of the individual tumors is anticipated to further improve the results of radiotherapy by tailoring dose and treatment schedule, by combining radiotherapy with modern drugs, and by consideration of intratumoral heterogeneity based on biological imaging. Improvement of local tumor control by these biology-driven approaches is expected to contribute significantly to improved survival.

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