Most cancer patients will require radiation therapy some time during their disease. Thirty percent to 50% of all radiation treatments are palliative, either to alleviate symptoms or prophylactic to prevent deterioration of quality of life from local progressive disease. Radiotherapy is a locally effective tool. It typically causes no systemic and mostly mild acute side effects. We will provide an overview of principles, decision-making, and new developments in palliative radiation therapy. © Semin Oncol 38:443-449 © 2011 Elsevier Inc. All rights reserved.

The majority of cancer patients receive one or several radiotherapy treatments throughout their disease. Up to 80% of patients benefit. Radiotherapy not only reduces the size of the tumor or relieves symptoms; low-dose radiotherapy also has anti-inflammatory, anti-secretory, anti-edematous, and analgesic effects. Local radiotherapy is efficient and safe, has few side effects, and is cost-effective.

AIMS OF PALLIATIVE THERAPEUTIC RADIOThERAPY

A distinction is made between different aims of therapy in palliative radiotherapy. Palliative radiotherapy can be carried out in a purely symptom-oriented manner or directed toward signs of tumor disease. In both situations, quality of life is the most important consideration.

Symptom-Oriented Palliative Radiotherapy

Palliative symptom-oriented radiotherapy aims to alleviate symptoms like pain, distress, dysphagia, paresis, or unpleasant smells. Side effects are avoided and stress during treatment is kept as low as possible. The underlying disease is usually not influenced.

Signs-Oriented Palliative Radiotherapy

Palliative signs-oriented radiotherapy aims to achieve (temporary) local control, avoid future symptoms and complications, and prolong life. Side effects are accepted to a certain extent (Figure 1).

METHODS AND TREATMENTS

Since the beginning of the 20th century, irradiation has been used for cancer treatment. It is usually done with a linear accelerator and high-energy photons or electrons. In a palliative situation, direct adjustment of the irradiation fields at the accelerator is possible. Complex target volumes require computed tomography (CT)-based three-dimensional (3D) planning. Modern high-precision radiotherapy techniques that require relatively long treatment sessions like stereotactic radiation therapy and intensity-modulated radiation therapy are usually reserved for patients with favorable performance status.

The fractionation schedule depends on the patient’s performance status and prognosis. For conventional fractionation, daily fractions of 1.8–2.0 Gy are given 5 days per week. By increasing doses per fraction (hypo-fractionation), the treatment period can be shortened with mostly an equivalent effect. The effect may not last as long as conventional fractionation and the risk of late effects increases. Therefore, hypofractionated radiotherapy is more often used for those with a limited life expectancy.

Prediction of prognosis is essential for selection of an appropriate fractionation schedule for the individual. Physicians make correct prognoses in 20% to 60% of cases. The prognosis for those who live less than 4 weeks is mostly too optimistic, and the survival time of the small group of long-term survivors (15%–20%) is
Planning palliative radiotherapy for patients who have many physical problems to be taken into account requires incorporation of supportive measures. Internationally well-established standardized instruments to record symptoms and determine quality of life can facilitate medical decision-making and assessment of treatment success. During this process, individual stress should be determined, as this does not necessarily correlate with symptom intensity. Stress from limitations in everyday life (psychosocial, existential, and financial problems) and those caused by medical and nursing actions or processes are usually underestimated. This particularly applies to patients with a short life expectancy (<6–12 weeks). These new findings should be considered more carefully when treatment decisions are made. Early palliative care, which can improve not only quality of life but also survival, is an option. Shared decision-making is an additional option. The importance of shared decision-making has now been recognized by the healthcare sector. The “Nationaler Krebsplan” (National Cancer Plan) was founded 2 years ago, supported by the German Federal Ministry of Health. The initiative examines this topic in special work groups. Special training programs are being developed to enable patients and medical staff to follow the principles of shared decision-making.

Patient surveys have shown that shared decision-making is possible and required in palliative radiotherapy. People with bone metastases who have relatively good performance are more likely to choose fractionated radiotherapy despite the longer overall treatment time. This is because of the expected lower risk of fracture and less frequent need of re-irradiation. A decision board has been employed to decide between two treatments for advanced lung cancer (2 x 8, 5 Gy 1x/wk v 13 x 3Gy on working days). Fifty-five percent of patients chose the longer treatment scheme because of longer expected survival time and better local control. Short-term irradiation was chosen because it requires less time, is more cost-effective, and symptoms can be better monitored. Of those who chose short-term therapy, 56% received fractionated radiotherapy. For percent of those who chose the fractionated concept were treated with a short-term therapy. The deviation from individual preferences had no effect on satisfaction related to the decision-making process. Further studies are required.

BRAIN METASTASES

Brain metastases occur in up to 40% of all cancer patients (predominantly breast and lung cancer). These numbers are growing, particularly because patients live until cerebral metastases occur due to improved sys-
temic therapies. The prognosis for multiple brain metastases is about only 4 weeks if untreated.

The choice of treatment depends on whether brain metastases are solitary or multiple and on the patient’s recursive partitioning analysis (RPA, see above) class. Those with a Karnofsky index of 70% or more, without extracerebral metastases, and with a controlled primary tumor (RPA class 1) have the best prognosis. Average life expectancy is 7 months. Patients with a Karnofsky index < 70% (RPA class III) have a prognosis of only 2 months. People in RPA class II are also in good general condition (Karnofsky index ≥70%). However, they have at least one other unfavorable prognostic factor (older than 65 years, extracranial metastases, and/or one uncontrolled primary tumor). In these patients, median survival time is 4 months.20 The German Society for Radiation Oncology has published a guideline for radiotherapy of brain metastases and leptomeningeal carcinomatosis.21

Single brain metastases verified by magnetic resonance scan (because a CT scan is less sensitive) are

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Prognosis and Indications</th>
<th>Duration of Therapy</th>
<th>Response Rate</th>
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</table>
| 1 x 8 Gy | Prognosis: life expectancy <3 mo  
—painful uncomplicated bone metastases | 1 d | 60%–90% |
| 2 x 7.5 Gy | Prognosis: life expectancy only a few weeks  
—bronchogenic carcinoma with bronchial occlusion/compression | 1 wk | 30%–90% |
| 4–6 x 0.5–1 Gy | Inhibition of inflammation | 1 wk | 70%–90% |
| 5 x 3–4 Gy | Prognosis: life expectancy <3–6 mo  
—bone metastases affecting soft tissue  
—metastatic bronchogenic carcinoma with imminent bronchial occlusion / bleeding,  
—ulcerated or painful metastases in soft tissue  
—multiple brain metastases, poor general condition and uncontrolled extracranial tumor manifestations | 1 wk | 60%–90% |
| 10 x 3 Gy | Prognosis: life expectancy <1 year  
—bone metastases with the aim of recalcification  
—advanced bronchogenic carcinoma  
—multiple brain metastases, Karnofsky index >70 % | 2 wks | 60%–90% |
| 13–15 x 3 Gy | Prognosis: life expectancy not very much longer than 1 year  
—bone metastases without any further tumor manifestations  
—advanced bronchogenic carcinoma, reasonable general condition, comorbidities | 3 wks | 60%–90% |
| 20–30 x 2 Gy | Prognosis: life expectancy >1 year  
—advanced bronchogenic carcinoma stage III and good general condition (possibly also in the form of palliative radiochemotherapy) | 4–6 wks | 60%–90% |
| 20–30 x 2–3 Gy IMRT | Patients in sufficient general condition with advanced tumors, re-irradiation, Patients in good general condition with, eg, isolated paraspinal metastases, isolated vertebral metastases affecting intraspinal areas | 5–6 wks | 65%–90% |
| 1–3 x 12–26 Gy stereotaxy | Patients in good general condition with individual/few solitary or singular brain metastases  
Individual/few solitary lung or liver metastases | max. 1 wk | 70%–90% |

Abbreviation: IMRT, intensity-modulated radiation therapy.
usually treated with neurosurgery or radiosurgery depending on their size and localization. Local control should be followed by whole-brain irradiation. Radiosurgery is used for up to three or four brain metastases, up to diameters of 3.5 cm. In up to 90% of single/solitary brain metastases that are asymptomatic or respond well to dexamethasone, long-term local control can be achieved with single-fraction radiosurgery. In larger metastases (≥4 cm), fractionated stereotactic radiotherapy minimizes the risk of perifocal edema and necrosis. Re-treatment is possible in recurrences.

Patients with multiple brain metastases usually receive whole-brain irradiation alone. Subsequently, 75% to 80% experience improvement of pre-existing neurological symptomatology. There is no reason to believe that an escalation of the total dose beyond 30 Gy improves overall survival and intracerebral control. In patients with brain metastases from a relatively radioresistant tumor such as malignant melanoma, colorectal cancer, or renal cell carcinoma, such a dose-escalation can improve treatment outcomes.22–24

Short-course radiation (5 x 4 Gy in 1 week) does not result in a worse prognosis when compared to 30 Gy in 10 fractions. There are indications that the risk of radiogenic long-term consequences like neurocognitive deficits increases with doses per fraction of 3 Gy or higher. Hypofractionated short-course regimens such as 5 x 4 Gy are recommended for those with a Karnofsky index <70% (RPA class III) and/or with several visceral metastases (Figure 2).

Potential side effects of irradiation (intracranial pressure with nausea and vomiting) can be sufficiently controlled with prophylactic cortisone. Prophylactic anticonvulsive therapy does not have any advantages, and is only recommended if symptoms are present.

Apart from the RPA classification, there are two other scores for determination of prognosis.10,11 The following factors are relevant to prognosis: age, general health, number of brain metastases, extracranial metastases at the time of whole-brain irradiation, and interval from first diagnosis of the malignant disease to diagnosis of brain metastases.

For patients with the best prognosis, long-term radiation with conventional fractionation is recommended. These schedules are less likely to result in neurocognitive deficits. Prognostic scores are not a substitute for individual decision-making.

Figure 2. Pathway brain metastases.21 KPS = Karnofsky performance score; WBRT = whole-brain radiation therapy.
BONE METASTASES

Bone metastases represent the most frequent indication. They occur especially in advanced breast, lung, or prostate cancer. Bone metastases can be osteolytic, osteoblastic, or mixed. In spite of their higher radiodensity, osteoblastic metastases are not considered stable in general. Regardless of their type, osseous metastases involve clinical symptoms and risks, which depend on their localization. Slowly increasing ostealgia that is hard to localize is most frequent. Radiotherapy of bone metastases is performed to relieve pain, restabilize the osteolytic bone, or minimize the risk of paraplegia. The American College of Radiology Appropriateness Criteria Expert Panel on Radiation Oncology has published guidelines for the irradiation of bone metastases. Addition bisphosphonates for pain relief and for recalcification is reasonable and should be discussed considering the prognosis.

Purely symptom-oriented irradiation of bone metastases to relieve pain in regions that have not received preoperative irradiation can be performed with 1 x 8 Gy. A meta-analysis has shown that one-time irradiation of uncomplicated bone metastases (no fracture, no neurological deficits) is as effective as fractionated irradiation relating to analgesia without intensifying toxicity. In up to 70% to 80% of patients, significant pain relief can be achieved. This pain relief results in both an improved quality of life and a significant reduction of pain medication. For this purpose, a standardized pain assessment is adjusted individually to prevent an over- or underdose. Pain medication has to be administered concurrently with radiotherapy.

Fractionated radiotherapy is significantly more effective than single-fraction radiotherapy with respect to restabilization and avoiding fractures. However, it is noteworthy that significant increases in bone density are not visible until after 4 to 6 months.

OBSTRUCTION AND COMPRESSION SYNDROMES

Superior vena cava syndrome is one indication that requires urgent radiotherapy, but if this condition is apparent before or at the time of cancer diagnosis, an attempt should be made to secure a histologic diagnosis before initiating radiotherapy. This is because in some lymphomas, germinative tumors, and small cell lung cancers, disease-oriented chemotherapy is more rational. In 60% to 80% of patients, a palliative effect can be achieved (improvement of results, symptom relief). For selected patients, brachytherapy allows the application of high doses per fraction and a rapid relief of symptoms. The surrounding normal tissue is only slightly affected. If brachytherapy is not possible or indicated, irradiation is performed as external-beam radiotherapy. Radiotherapy should start as soon as possible; initially, a simple technique and higher doses per fraction may be used. After a few fractions, this technique is replaced by 3D-conformal CT-based radiotherapy to prevent late damage to heart, lungs, and spinal cord. Corticosteroids are administered concurrently with radiotherapy.

Spinal Cord Compression

Intraspinal metastases or infiltration of the spinal cord by vertebral metastases can lead to spinal cord compression with motor and sensory deficits and pain. Radiotherapy should be started promptly, ie, within 24 hours from the first presentation. Anti-edematous treatment with corticosteroids should be started immediately.

Neurosurgical or orthopedic evaluation before radiotherapy should be considered for selected patients. The following 10% to 15% of all patients with spinal cord compression are likely to benefit from surgery and postoperative irradiation. Disease-oriented chemotherapy is more rational. In 60% to 80% of patients, a palliative effect can be achieved (improvement of results, symptom relief). For selected patients, brachytherapy allows the application of high doses per fraction and a rapid relief of symptoms. For this purpose, a standardized pain assessment is recommended.

Twenty-two percent of patients need re-irradiation after single-fraction radiotherapy because of recurring pain, compared to 7% after fractionated radiotherapy. In a more recent meta-analysis of 5,000 patients, the rate of pathological fractures was similar after single-fraction and fractionated radiotherapy (3% vs 2.8%). In recurrent pain, repeated radiotherapy has the same relieving effect in 63% of patients as the first irradiation dose.

Fractionated radiotherapy is significantly more effective than single-fraction radiotherapy with respect to restabilization and avoiding fractures. However, it is noteworthy that significant increases in bone density are not visible until after 4 to 6 months.
who have a poor performance status and small chances of improvement of neurological symptoms should be treated with hypofractionated short-course schemes such as 5 × 4 Gy in 1 week. In relatively good survival prognosis, longer-course radiotherapy with higher total doses (10 × 3 Gy in 2 weeks or 20 × 2 Gy in 4 weeks) should be used.37

**Bleeding, Ulceration, and Swelling**

Tumor bleeding often determines the prognosis after vessel erosion. Bleeding of the tumor can be stopped by short-course radiotherapy with higher doses per fraction. Common indications for palliative radiotherapy are large carcinomas of the cervix or corpus uteri associated with vaginal bleeding, ulcerated bleeding breast cancers, skin tumors or metastases, lung cancers with hemoptysis, and occasionally also bleeding bladder or rectal cancers.

In a bleeding tumor, radiotherapy is mostly started with higher doses per fraction (3–5 Gy) if required and then continued with conventionally fractionated radiotherapy, possibly in combination with palliative chemotherapy. Usually, tumor bleeding stops within 24 to 48 hours after the beginning of irradiation or after a biologically effective dose of 20 Gy. The more elaborate three-field approach yields considerably better results than the opposing-field approach in cervical or corpus uteri associated with vaginal bleeding, ulcerated bleeding breast cancers, skin tumors or metastases, lung cancers with hemoptysis, and occasionally also bleeding bladder or rectal cancers.

SUMMARY AND CONCLUSION

In palliative medicine, radiotherapy is an important option. Both rapid and long-term effects associated with very low treatment-related toxicity can be achieved. Furthermore, radiotherapy is important for oncological emergencies like symptoms due to obstruction/compression, tumor bleeding, and spinal cord compression. Dose-fractionation and type of radiotherapy must be tailored individually taking into account the goal of treatment, localization of the tumor manifestations, and the patient’s prognosis. In limited life expectancy, irradiation should be performed with higher doses per fraction and a short overall treatment time. Selection of the individual palliative treatment concept (including radiotherapy) should be performed by a multidisciplinary and multiprofessional team. The patients or the patients and their relatives should participate in decisions. The options that radiotherapy can offer for patients in a palliative situation appear to be underestimated. Closer cooperation between patients, relatives, radiation oncologists, other physicians, and other members of palliative teams is required to achieve the maximum benefit from radiotherapy for patients in a palliative situation.

REFERENCES