Radiotherapy in cancer pain management

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Epidemiology of pain in oncology and radiotherapy

Pain is a common symptom in the natural history of cancer. It can be present during the initial phase of the disease, especially in certain tumour locations (e.g. bone, central nervous system, pancreas, and lung). It is more frequent in locally recurrent or metastatic disease. Most cancer patients experience pain, usually of moderate to severe intensity, and also have a number of distinct pain types. The commonest situation responsible for pain is bone metastases. In metastatic or recurrent malignant disease, pain of different intensity is present in 50–70% of cases, of which 75% are directly attributable to the malignancy [1–5]. Careful clinical evaluation of pain is an essential part of the global management of the cancer patients; this can be difficult in some special situations, as in elderly patients. An objective measurement of pain intensity is necessary, and can be performed most of the time with a visual analgesic scale [6].

The management of pain is a team approach between specialists in chemotherapy, radiotherapy, surgery and anaesthesiology and supportive care, but also psychologists and physiotherapists. For example, the conventional symptomatic treatment of metastatic bone pain requires the use of multidisciplinary therapies, such as analgesic medication (from level 1 to level 3, non-opioid and opioid analgesics, and also tricyclic antidepressants, anticonvulsive, psychotropic drugs, non-steroidal anti-inflammatory drugs, corticosteroids, bisphosphonates) in association with radiotherapy, chemotherapy or hormonotherapy depending on the primary site [7].

Radiotherapy is playing an important role in pain control in association with these other approaches. In a standard radiotherapy department, approximately 15% of patients are referred for pain relief. The most frequent clinical situation is to provide pain relief for painful bone metastases and for three-quarters of patients who achieve pain relief, half will remain free from pain. In 80% of patients, the primary cancer is originating from breast, lung, kidney and prostate [8]. The median survival time after appearance of bone metastases is between 2 and 4 years for patients with breast, prostate and thyroid cancers. The prognosis for lung cancer is shorter, usually less than one year. Between 5% and 40% of patients will be alive at 5 years (Table 1). The metastases may involve vertebrae, long bones, the pelvis or skull [9]. Approximately 65% of patients with skeletal disease suffer from bone pain [10]. Associated to pain, cancer patients also suffer from symptoms like anorexia, asthenia, nausea, vomiting, insomnia, and all these symptoms have to be treated contemporarily [11].

Other main indications of radiotherapy in cancer pain management are fractures due to bones metastases, spinal cord compression, multiple myeloma, brain metastases, primary tumours (e.g. pancreatic carcinoma, Pancoast tumours, recurrent pelvic tumours) and benign diseases (e.g. peritendinitis, heel spur, degenerative osteoarthritis), which will not be covered in this review.

It is important to remember that if radiotherapy is effective to control pain, it can be also responsible for painful conditions like osteoradionecrosis of the mandible, soft tissue necrosis of the oral cavity or anal canal, and radiation plexopathy.

Pathophysiology of cancer pain

Cancer pain is due to different mechanisms, but most of the time it is related to direct tumour infiltration. These somatic and visceral pains result from activation of nociceptors by tumour infiltration of tissues, and from secondary inflammatory changes with release of algesic chemicals that act to sensitize nociceptors [14]. The management of such pain is performed through treatment targeted at the tumour

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Table 1
Results of two recent randomized trials comparing single-fraction radiotherapy vs. multiple fractions

Trial	Schedule	pts	Pain relief	Complete response	Progression	Retreatment	Pathological fracture
Bone Pain Trial Working Party [12], 1999	1 × 8 Gy	383	78%	57%	34%	23%	7 patients
	5 × 4 Gy	378	78%	58%	30%	10%	9 patients
	10 × 3 Gy					$p < 0.001$	$p = 0.2$
Dutch Bone metastasis study [13], 1999	1 × 8 Gy	585	72%	37%	52%	25%	24 patients (4%)
	6 × 4 Gy	586	69%	33%	46%	7%	10 patients (2%)
						$p < 0.0001$	$p < 0.05$

(chemotherapy, surgery, or radiotherapy) and analgesic drugs (non-opioid, opioid) [15].

Deafferentation pain is maybe another mechanism and is related to injury and infiltration of peripheral nerves [15]. This pain is difficult to control, and may continue after treating the cause.

The pathophysiology of pain due to bone invasion is complex, and can be due to nerve compression, or muscle contractions. The proliferation of malignant cells increases the pressure in the bone, leading to increased pain. In such cases, the main mechanism is somatic pain by nociception. Radiotherapy on this proliferation is very effective, by reducing the number of tumour cells, which decreases pressure and pain in the bone [16]. In some patients, the rapid pain response to the radiotherapy is related to inactivation or killing of inflammatory cells.

Radiotherapy of bone pain

Bone metastases

Single-fraction technique

Approximately 65% of patients with skeletal metastatic disease suffer from significant pain. One-third of patients with breast or prostate cancer and two-thirds of those with lung cancer will develop metastatic bone disease [17]. It is very common in a radiotherapy department where it can represent 10 to 20% of treatments. Radiotherapy is considered as a very effective treatment to control pain. A decade ago, the standard technique for bone metastases was an accelerated schedule of 5–10 fractions, delivering 20 Gy/5 fractions or 30 Gy/10 fractions over a period of 1 or 2 weeks [18]. Many recent randomised trials have compared such accelerated fractionated schedule with a single fraction delivering usually 8 Gy.

The randomised trial of the Bone Pain Trial Working Party, comparing a single-fraction of 8 Gy with multifraction doses, analysed overall survival, time to progression, time to first pain relief and complete pain relief (Table 1). In this trial, 681 patients were included between 1992 and 1997 with a follow-up over one year. The single-fraction delivered 8 Gy in 1 fraction over 1 day. Most of the patients (98%) allocated to a multifraction schedule received 20 Gy in 5 fractions over 5 days. The others (2%) received 30 Gy in 10 fractions over 10 days. Overall 78% of patients who could be evaluated experienced pain relief in both groups, and 57% in the single-fraction group vs. 58% in the multifraction group experienced a complete response. However, 23% of patients randomised to the single-fraction schedule were retreated, compared to 10% on the multifraction regimen ($p < 0.001$). No difference in time to progression and overall survival was observed [12].

The Dutch Bone Metastasis Study randomised 1171 patients with painful bone metastasis to receive either 8 Gy in 1 fraction or 24 Gy (4 Gy in 6 fractions). Both regimens were equivalent in term of palliation: rate of response and of complete response were respectively 69% and 33% in the multifraction group and 72% and 37% in the single-fraction group. Median time to pain progression was 24 weeks in the 4 Gy × 6 arm and 20 weeks in the 8 Gy × 1 arm. There was an effect of primary tumour type: breast cancer did better than prostate, lung or other cancer patients, with median time to progression of 36 weeks, 20 weeks, 10 weeks and 8 weeks, respectively ($p < 0.0001$). Retreatment was 25% in the 8 Gy × 1 group and 7% in the 4 Gy × 6 arm (Table 1) and it took place at an earlier stage in the 8 Gy × 1 group. More fractures were observed in the single-fraction than in the multifraction schedule (4% vs. 2%, $p < 0.05$) [13].

A study evaluated remineralization of lytic lesions after radiotherapy, using CT density measurement. After 6 months of follow up, bone density was significantly increased by an average of 173% after 30 Gy in 10 fractions, compared with an average increase of 120% after 8 Gy in single fractions [19].

The meta-analysis of Wu has reviewed the published literature on dose fractionation in local radiotherapy, to determine the schedule for painful bone metastases between 1966 and 2000. It divided published reports into three categories: comparison of single-fraction vs. single-fraction, comparison of single-fraction vs. multifraction radiotherapy, and comparison of different doses of multifraction radiotherapy. Analysis of trials with different single-fraction doses showed that response rates were lower with 4 Gy, but were similar with 6 Gy and 8 Gy, suggesting the absence of dose-effect relationship for total doses >4 Gy. No difference was found between different fractionation schedules (single-fraction vs. multifraction or multifraction vs. multifraction). No dose–response relationship, no difference among dose-fractionation schedules, no median duration of response (between 11 and 24 weeks), and no difference of toxicities were found between different schedules. The median time for pain relief after treatment was 3 weeks and the median actuarial duration of pain control was between 4 and 5 months, with two thirds of the patients experiencing complete pain control. This review concluded that it was recommended to use single-fraction dose radiotherapy with 8 Gy for painful bone metastases [20].

Pain flare following radiotherapy has been reported. A prospective evaluation of pain in 88 patients showed that 14% of patients who received a single fraction treatment had a pain flare on day 1 and 15% of patients who received multiple-dose fractions had a pain flare on day 1 but remaining in the range of 10–20% during the treatment [21].

In conclusion, randomized trials showed no significant difference between single and multiple fractions schedules for painful bone metastases, and confirmed the efficacy of the short-term schedule of 8 Gy in 1 fraction.

Retreatment after irradiation

Both the Dutch Bone Metastasis Study and the Bone Trial Working Party showed a significantly higher rate of retreatment in the single-fraction arm, but this could be due to a bias: it is considered more dangerous for radiation toxicity to give a second irradiation after 20 or 30 Gy, than after a single dose of 8 Gy and physicians are more willing to retreat after a single fraction. Analysis of the retreated patients in the Dutch Bone Metastasis Study showed that response to retreatment was 66% in the single-fraction group and 46% in the multifraction group ($p = 0.12$, ns). Time to response was not different in both groups, but the mean duration of remission was substantially longer in initial single-fraction patients (16 weeks vs. 8 weeks). Prostate cancer experienced the lowest response rate of retreatment (43%). No major difference in toxicity was observed. The authors conclude that with or without the effect of retreatment, single-fraction and multifraction radiotherapy provide equal palliation for painful bone metastases [22].

Cost analysis

In a radiotherapy department, the cost model results from three cost categories: series, fractions and Gy. A cost analysis of the Dutch trial was performed. The cost for a single-fraction schedule includes the cost per series, the cost per fraction, and 8 times the cost per Gy. In the same way, the cost of a multifraction schedule delivering 24 Gy over 6 fractions includes the price of one series, 6 times the price per fraction, and 24 times the cost per Gy. In this trial, the single-fraction schedule is less expensive than the multifraction one [23].

Controversies in single-fraction schedule

Pain relief, overall survival, quality of life and toxicity are equivalent between single- and multifraction radiotherapy. Moreover, the single fraction is more convenient to patients with metastatic bone pain, with less time spent in hospital, fewer constraints, and it is easier to implement into a radiotherapy department. However, the higher rate of fracture and retreatment in the single-fraction schedule cannot be ignored. Considering advantages and disadvantages of single- and multifractionation schedule, what could be the patients' choice? A study tried to assess an answer to this question, offering to patients the choice between two fractionation schedules: 24 Gy in six fractions vs. 8 Gy in one fraction. Sixty-two patients were informed on advantages and disadvantages of these two schedules and were asked to choose a fractionation schedule, to give a reason for their choice and to indicate the level of satisfaction with being involved in decision making. 85% preferred 24 Gy in 6 fractions over 8 Gy in one fraction ($p < 0.0005$). Multifractionation was chosen for the lower retreatment rate (92%) and fewer fractures (32%). Single-fraction was chosen for cost (11%) and convenience (89%) [24]. Another study evaluating patient' s preference between 20 Gy in 5 fractions vs. 8 Gy in one fraction in 101 patients showed opposite results. 72% preferred the single-fraction schedule [25]. In conclusion, single-fraction radiotherapy (8 Gy in one fraction) can be considered in most patients as the standard palliative treatment for cancer patients with painful bone metastases. When large volumes (including small bowel or lung)

GLENOID CAVITY OF THE SCAPULO-HUMERAL JOINT METASTASIS

Techniques: • patient supine
• two parallel opposed fields AP/ PA
• photon X ≥ 6 MV

Simulation: simulator or 2D dosimetric display.

Field: • 8 cm x 12 cm.

Dose: • 8 Gy in 1 fraction, with equal loading between both fields (4 Gy + 4 Gy) calculated at mid-plane.

Other possible technique: one single anterior field with photon X>15 MV, and dose of 8 Gy calculated at the level of the given dose (close to 3 cm).

Field of irradiation on simulator:

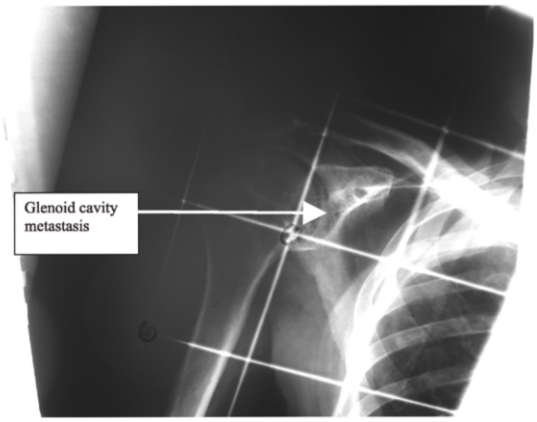


Fig. 1.

FEMORAL METASTASES

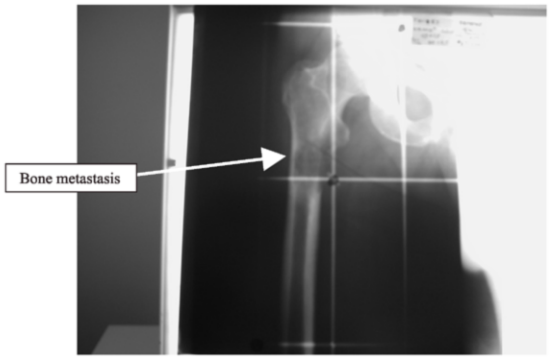
Techniques: • patient supine.
• two parallel opposed fields AP and PA.
• photon X> 6 MV.

Simulation: • simulator or 2D dosimetric display.

Field: • 10 cm x 16 cm.

Dose: • 8 Gy in 1 fraction, with equal loading between both fields (4 Gy + 4 Gy) calculated at mid-plane.
• 13 Gy in 2 fractions, with equal loading between both fields (6.5 Gy + 6.5 Gy) calculated at mid-plane.
• due to the diameter of the hip (> 14 cm), a single anterior field is not recommended.

Field of irradiation on simulator:



NB: Nail surgery can be proposed, due to the high risk of fracture.

Fig. 2.

LUMBAR BONE METASTASES

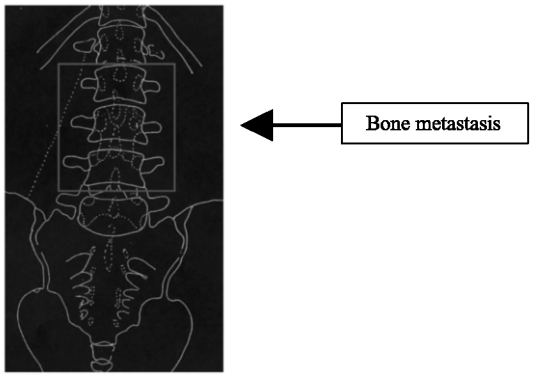
Techniques: • patient supine.
• two parallel opposed fields AP and PA.
• photon X > 8 MV.

Simulation: • simulator or 2D dosimetric display.

Field: • one vertebra above and below the metastatic vertebra.
• 10 cm x 9 cm.

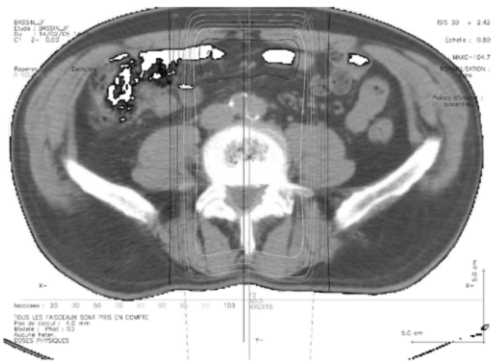
Dose: • 8 Gy in 1 fraction, with equal loading between both fields (4 Gy + 4 Gy) calculated at midplane.

Field of irradiation on simulator:



NB: CT can be useful to assess the extension of the vertebral metastases in the surrounding soft tissues, which can lead to an increase in the width of the field.

2D dosimetric display with the isodoses of irradiation:



NB: a different loading of the irradiation can be proposed to slightly reduce the dose in the abdomen (posterior field 5 Gy, anterior field 3 Gy). It should be noted that the anterior part of the vertebra is at the midplane.

Fig. 3.

SPINAL CORD COMPRESSION WITH EPIDURAL METASTASIS

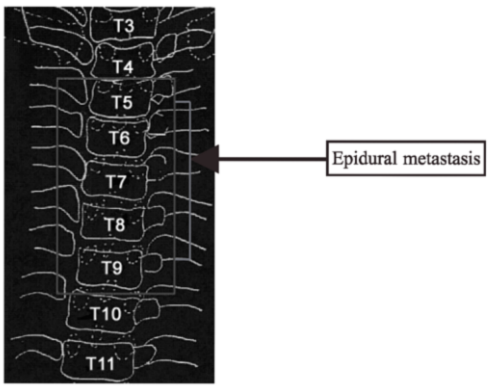
Techniques: • patient supine.
• two parallel opposed fields AP and PA.
• photon X > 8 MV.

Simulation: • simulator or 2D dosimetric display.

Field: • two vertebras above and below the metastatic vertebra.
• 16 cm x 9 cm.

Dose: • 8 Gy in 1 fraction, with equal loading between both fields (4 Gy + 4 Gy) calculated at mid-plane or:
• 20 Gy in 5 fractions, with equal loading between both fields (2 Gy + 2 Gy) calculated at mid-plane, can also be proposed.

Field of irradiation on simulator:



NB: MRI shows an epidural metastatis-extending between T6 to T8.

Fig. 4.

RIB METASTASIS

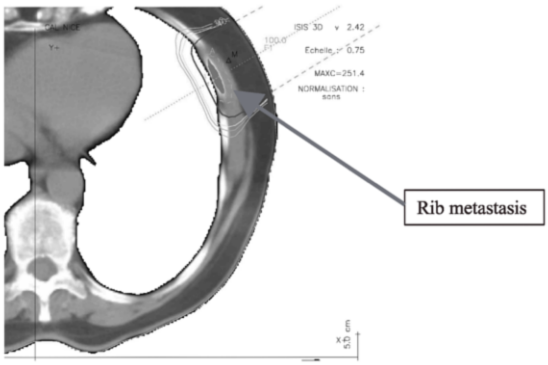
Techniques: • patient supine.
• one single lateral field.
• electrons: 12 MeV.
• depth of 3 cm.

Simulation: • simulator or 2D dosimetric display.

Field: • 7 cm x 6 cm.

Dose: • 8 Gy in 1 fraction, calculated on the 90% isodose.

2D dosimetric display with the isodoses of irradiation:



NB: it must be remembered that the dose distribution of electrons in air is not very accurate with most of the software used for treatment planning, the dose in the lung is not known with accuracy with electrons.

Fig. 6.

SACRO-ILIAC JOINT METASTASIS

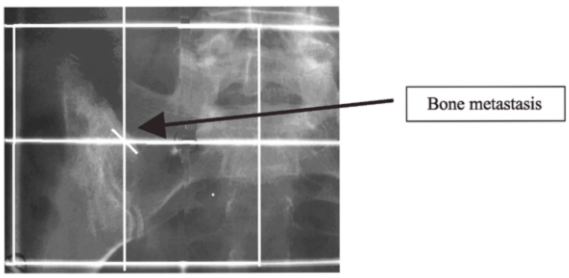
Techniques: • patient supine.
• three fields: two parallel lateral opposed and one posterior (wedges).
• photon X > 8 MV.

Simulation: • simulator or 2D dosimetric display.

Field: • 11 cm × 9 cm

Dose: • 20 Gy in 5 fractions: 1.5 Gy for each lateral fields, and 1 Gy for the posterior one.

Field of irradiation on simulator:



2D dosimetric display with the isodoses of irradiation:

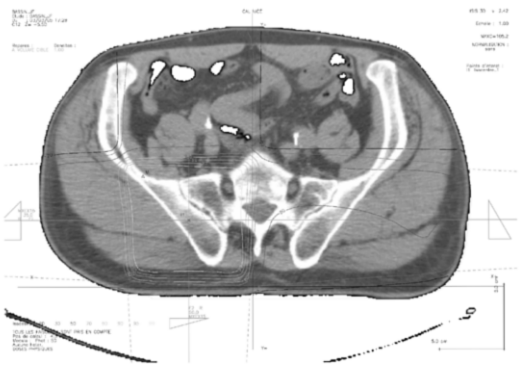


Fig. 5.

are included in the irradiation fields, especially in frail, debilitated patients, it can be safer to use a fractionated schedule. Patients should be informed and involved in therapeutic decision. Dose per fraction of 4 or 5 Gy can be given in such a case for a total dose of 10–20 Gy.

Some treatment techniques for bone metastases are presented in Figs. 1 through 6.

Neuropathic pain due to bone metastases

None of the studies evaluating radiotherapy for painful bone metastases classified pain to underlying aetiology (e.g. mechanical vs. non-mechanical, neuropathic component). Neuropathic pain refers to a pain or dysaesthesia with a radiating cutaneous component in the distribution of spinal nerves or peripheral

Table 2
Results of retrospective analysis of Rades et al. [27], comparing 5 schedules of radiotherapy in spinal cord compression

Schedule	8 Gy: 1 × 8 Gy	20 Gy: 5 × 4 Gy	30 Gy: 10 × 3 Gy	30 Gy: 15 × 2.5 Gy	40 Gy: 20 × 2 Gy	p-value
Patients	261	279	274	233	257	–
Motor function improved	26%	28%	27%	31%	28%	ns
Post treatment ambulatory rate	69%	68%	63%	66%	74%	ns
In field recurrence at 2 years	24%	26%	14%	9%	7%	<0.001

nerves. A recent study randomised 272 patients to receive 8 Gy in one fraction or 20 Gy in 5 fractions. Overall response rate was 53% and 61% for single and multiple fractions respectively. Time to treatment failure was 2.4 vs. 3.3 months. Although it did not achieve statistical significance, single-fraction was not shown to be as effective as multiplefraction. The authors conclude that 20 Gy in 5 fractions should be recommended for neuropathic pain due to bone metastases [26].

Spinal cord compression

In the case of spinal cord compression, neurological deficit with the risk of paraplegia is the main issue. Surgery and radiotherapy are effective treatments. Radiotherapy is aimed at controlling cancer cells, usually infiltrating the epidural tissue. If pain is present, it can be due to direct bone invasion from a metastatic, or primary tumour, or perineural infiltration. Radiotherapy is playing an important role to control pain, often in an emergency situation, and prevent evolution toward total paraplegia.

The optimal treatment for patients with metastatic spinal cord compression is still being debated. Rades retrospectively evaluated several schedules: 1 × 8 Gy, 5 × 4 Gy, 10 × 3 Gy, 15 × 2.5 Gy, 20 × 2 Gy. These five radiotherapy schedules provided similar functional outcome and post-treatment ambulatory rate (Table 2). 26% of patients who were not ambulatory before radiotherapy regained the ability to walk [27]. To minimize treatment time, the authors recommend 1 × 8 Gy for patients with poor predicted survival and 10 × 3 Gy for other patients. The short course regimen of 8 Gy in one fraction was specifically evaluated in 199 patients with spinal chord compression. 27 patients had improved motor function, 26% regained walking ability and 29% of long-term survivors (>12 months) needed re-irradiation [28].

Only one randomized trial compared two schedules of fractionation in metastatic spinal cord compression. It included 276 patients with a short life expectancy randomly assigned to receive a short-course radiotherapy (2 × 8 Gy) or a split-course radiotherapy (3 × 5 Gy; 5 × 3 Gy). No significant difference in response, duration of response, survival or toxicity was found between the two arms. After radiotherapy, 56% of patients in the short course and 59% of patients in the split course had back pain relief, 68% and 71% were able to walk, and 90% and 89% had good bladder function. The authors recommend the short course regimen [29].

An example of irradiation technique for spinal cord compression is presented in Fig. 4.

Multiple myeloma

Myeloma and plasma cell tumours are radio-responding tumours, but the systemic nature of the disease in most patients limits the application of localized irradiation. In multiple myeloma, an effective palliation of pain control can be obtained by small fields and low doses of radiation. A retrospective study tried to define the minimum effective radiation dose for durable pain relief in 101 patients with multiple myeloma irradiated in 306 sites. Symptom relief was obtained in 92% of sites receiving a total dose less than 10 Gy and 98% of sites receiving 10 Gy or more. No dose–response relationship could be demonstrated [30]. Radiotherapy seems to be more effective during concomitant chemotherapy than without systemic treatment. A study of 70 patients showed that 80% of patients suffering from myeloma pain had complete pain relief with local radiotherapy and concurrent chemotherapy vs. 39% in patients receiving only radiotherapy [31]. Hemibody irradiation has been performed in the past for generalized pain due to multiple site involvement in multiple myeloma. A single fraction of 6 Gy is used for the upper body and 8 Gy for the lower body. It is rarely used today, due to toxicity.

Nowadays, most patients with multiple myeloma receive bisphosphonate. No clinical trial has compared radiotherapy with bisphosphonate in pain relief. Optimal uses of these two modalities require further

investigation, and a combined approach using the concept of additive effect and spatial cooperation should be investigated.

Radiotherapy of other painful cancers

Brain metastases

Brain metastases are a frequent complication in patients with solid tumours. The incidence varies between 20% and 30% [32]. The most frequent primary tumours are breast and lung. The incidence and symptoms of brain metastases are increasing, due to improvement of neurodiagnostic imaging, and the increased survival. Brain metastases are associated with pain in 60% of patients, due to intra-cerebral pressure. This is the most frequent symptom because of the nature of tumour growth and its surrounding oedema. The choice of the most adequate treatment depends on different prognostic factors [33]: number of metastases, type of primary cancer, status of systemic disease, performance and neurological status, and patient' s age.

When possible, surgery is the treatment of choice. The surgical treatment is recommended for the single, superficially located brain metastasis with intra-cranial pressure (ICP) in patients with good performance status. Radiosurgery can be performed when there is a small number of brain metastasis (up to 3). These treatments can be followed by whole-brain radiotherapy (WBRT) with an improvement of overall survival to 8–11 months [34,35]. In other patients, WBRT alone is recommended with a median survival extended to 3–5 months. The technique can be whole-brain irradiation, delivering 30 Gy in 10 fractions over two weeks, or a combination of whole-brain irradiation with a boost to the gross tumour. Radiosurgery (RS) is used when there are less than four brain metastases. It can be proposed for patients with inaccessible lesions or those with poor performance status. Overall survival is between 6 and 12 months [36,37]. For patients with good prognostic factors, RS can be used with WBRT. RS seems to be as efficacious as surgery to provide relief of neurological symptoms. RS can be an alternative to surgical resection. Corticosteroids are also very effective to palliate pain.

Pancoast syndrome

Radiotherapy is the standard treatment of pancoast syndrome. Tumours of the superior pulmonary sulcus, called pancoast tumours, are rare. Non-small cell lung carcinomas represent the most frequent cause of superior sulcus lesions, they represent 5% of all lung cancers. Pancoast tumours are presenting with constant pain, by invasion of the lower part of the brachial plexus, the intercostal nerves and the stellate ganglion (Horner' s syndrome). The distribution is from the shoulder and the scapula to the ulnar part of the arm, the elbow and finally to the ulnar distribution of the forearm, and the small and ring fingers of the hand.

In 1961 Shaw and Paulson [38] introduced pre-operative radiotherapy (30 to 45 Gy in four weeks, including the primary tumour, mediastinum and supra-clavicular region), followed by surgical resection. This radiosurgical approach became the treatment of choice for pancoast tumours, with a mean 5-year survival of approximately 30% [39]. Nevertheless, even if local disease control was achieved, distant relapses (brain, bones) were frequent. Neoadjuvant treatment using radiotherapy and chemotherapy before surgery, could increase the resectability of the pancoast tumour and pain control. Further chemotherapy could be proposed after surgery. The induction chemoradiation for Pancoast tumours improves the rate of complete resection and medium-term survival [40]. The surgical goal is en-bloc resection of the chest wall, with removal of the upper lung lobe in continuity of the ribs, vertebral transverse process, subclavian vessels, T1 nerve root, upper dorsal sympathetic chain, and prevertebral muscles.

Pancreatic carcinoma

Pancreatic cancer is a tumour with poor prognosis. Most patients with carcinoma of the pancreas are diagnosed in a non-resectable stage. The median survival in that stage is between 6 and 12 months. The main goal is to preserve quality of life, and reduce pain and complications due to local progression. Radiotherapy for pancreatic cancer is used to increase the median survival in patients with resectable or unresectable tumours. However, radiotherapy also has a palliative aim, by reducing the symptoms of local progression (gastro-intestinal obstruction, biliary obstruction, or splanchnic invasion). Pain affects most patients with pancreatic carcinoma. The incidence of pain varies between 50% and 97%. At a late stage of the disease, pain is present in nearly 90% of patients [41]. To control pain from locally advanced carcinoma of the pancreas, medical treatment, surgical procedure (surgical thoracoscopy), percutaneaous splanchnic-ectomy, or radiotherapy can be used. Radiotherapy can be given with external beam, or as intra-operative, or a combination of both [42,43]. The standard radiotherapy schedule consists of a total dose of

50 Gy, given in 1.8–2 Gy per fraction, over 5 weeks. Unfortunately, the radiotherapy treatment is limited by side effects to soft tissues, small bowel, liver and kidneys [44,45]. For patients excluded from standard concomitant chemoradiotherapy (age >75 years, local extension of the disease, hematologic defects) with unresectable disease, hypofractionated radiotherapy in pain relief is efficacious: 30 Gy in two weeks, 3 Gy per fraction, with a reduced need for analgesics [41].

Locally recurrent tumours

Locally recurrent tumours, especially in the pelvis (rectum, uterus, and bladder) are associated with pain. Radiotherapy can be proposed with either curative or palliative intent, but in most cases it is efficient for pain relief. The dose and field size depend on the various clinical situations.

Metabolic radiotherapy using radiopharmaceuticals

An alternative for delivering radiation to the skeleton is the use of systemic radiopharmaceuticals. Strontium-89 Chloride and Samarium-153 EDTMP are the most widely used.

Strontium-89 Chloride is a bone-seeking compound concentrated in the bone during osteoblast-induced bone mineralization, which behaves biologically like calcium. Strontium-89 is a beta-emitting radioisotope, with a physical half-life of 50.5 days and a maximum energy of 1.46 MeV. The usual therapeutic dose is 148 MBq. It is avidly taken up by osteoblastic metastatic prostatic cancer. It can palliate metastatic bone pain, and is as effective as external beam radiation. The main complication is bone marrow depression, so it is contraindicated in myelosuppressed patients. Samarium-153 is a radioisotope emitting beta particles, with a maximum energy of 0.8 MeV. It has a physical half-life of 1.9 days. Samarium-153 is targeted to the bone by conjugation with a phosphonate compound (EDTMP: ethylene-diamine-tetramethylene phosphonic acid). Strontium-89 Chloride and Samarium-153 EDTMP are concentrated in bone proportionally to osteoblastic activity.

The use of therapeutic radionuclides, which localize at metastatic sites, has been found to be an effective method for bone pain palliation, especially for multiple bone metastases. This treatment is mainly indicated for bone pain by prostate cancer metastases escaping to hormonotherapy. It is based on the injection of radioactive isotopes, which are taken up by bone metastases. Pain relief rates with Strontium-89 Chloride range from 60% to 84% [46–48]. The mean time to pain relief is about one month. The mean duration of relief is about 6 months. Patients can be retreated after 3 months, due to the longer half-life. With Samarium-153 EDTMP, pain relief is between 62% and 74% [49]. The mean duration of relief is about 4 months. The mean time to pain relief is usually shorter than with Strontium-89 Chloride (one week vs. one month), because the half-life of Sm153 is shorter. Patients can be retreated after two months. It remains possible to perform another external radiotherapy focalised on painful localisations, after treating the patient with internal approach.

Hemi–body irradiation

In case of diffuse bone metastases in various bone segments, upper or lower hemi-body irradiation (HBI) has been proposed. In some patients, both upper and lower HBI can be performed with careful matching of the adjacent limit of the fields. The radiation is given through a large anterior–posterior posterior–anterior (AP–PA) field to a dose of 6 Gy at mild pain. Pain relief is obtained in the majority of patients, but radiation toxicity can be important due to large volume irradiation (nausea, vomiting, diarrhea, and asthenia). With the development of modern medical analgesic treatment with opioids, HBI is becoming uncommon [50,51].

Conclusion

Pain management is a key aspect of global care for cancer patients. Pain control is often a multidisciplinary task involving different medical specialists. Medical treatment and psychosocial support are playing an increasing role especially in patients with advanced disease.

For localized pain, especially from bone metastases, origin radiotherapy is a single and efficient treatment. From randomized trials and evidence-based medicine it is, at the present time, recommended to deliver radiotherapy in a single- or few-fraction schedule. Radiation oncologists in collaboration with other specialists are playing an important role in palliating pain and improving the quality of life of cancer patients.

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