Local control of childhood and adult soft tissue sarcomas

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Introduction

Soft tissue sarcomas are rare tumours that account for approximately 5% and 1% of malignancies in children and adults, respectively. They comprise a wide variety of histological subtypes, although their respective proportions appear clearly different in both age groups: rhabdomyosarcomas (RMS) represent half of soft tissue sarcomas that occur in childhood, whereas malignant histiofibrosarcomas, liposarcomas, and leiomyosarcomas are the predominant ones in adulthood. This histological specificity largely explains differences in terms of tumour progression, radiosensitivity, chemosensitivity, and prognosis, and so also differences in therapeutic strategies. But that is not all, as evidenced by frequent divergences in the management of similar tumours by adult and paediatric oncological groups respectively. This exemplifies another key concept: the dramatic differences in the sensitivity to therapy of adult and immature normal tissues. It is noteworthy that chemotherapy plays a wider role in the local management as well as the prevention of distant seeding in children than in adults. Nonetheless "conventional" local treatments (i.e. surgery and radiotherapy) are closely related in both age groups, and preservation of physiological functions has become a primary concern for all patients, their families, and their oncologists, unless it compromises survival. Modern advances can benefit both groups. This work updates previous national/international projects that have evaluated the role of local treatment in adult and paediatric soft tissue sarcomas. Only selected articles (especially reviews, in English) are referenced. In order to clarify different strategies, we will assess levels of evidence, in which the strength of studies is ranked according to the study design (1 > 2 > 3).

ADULT: Treatment modalities in adult soft tissue sarcomas

Surgery

Biopsy [1,2]

This is the first critical step in the management of adult soft tissue sarcoma. It should be performed by a surgeon with experience in this field. This includes appropriate placement relative to the definitive site of resection, and choice of appropriate technique (fine-needle aspiration, core-needle biopsy, or open surgical biopsy). This choice depends on the surgeon's practice and his/her pathologist's experience. As far as deep-seated masses, only detectable on imaging, the help of the radiologist or the interventional radiologist can be requested, in order to obtain limited material. Care should be paid again to the placement of the needle track.

Surgical resection [2]

It remains the mainstay of local therapy. Table 1 summarises the outcome following an exclusive surgical management. Local control is in excess of 70%, although it depends upon the type of surgery, patient selection, and possibly tumour aggressiveness.

Amputation is a historical approach that yields less than 10% local failure, but at the price of considerable functional and cosmetic deficit. Type of amputation is conditioned by the tumour site, and by the need to take out generally one joint above the tumour: below-knee for foot, above-knee for leg, hip disarticulation in proximal thigh, hemi-pelvectomy preserving or not the limb, radical scapulectomy, and forequarter amputation preserving or not the upper extremity. Nowadays, its indications remain generally confined to local failures following an initial heavy treatment, to extensive lesions requesting major nervous or vascular sacrifice, and to selected lower extremity lesions in which conservative surgery and radiation-induced complications are likely to compromise the functional outcome. Furthermore, it was

Table 1
Exclusive surgical resection in soft tissue sarcomas in adults (only references mentioned in the text are listed in the reference section)

Author (*journal*), year	No. of patients	% Amputation	% Local failures	Survival	Prognostic factors
Cantin (*Ann Surg*), 1968	653	?	29	61	size, adequacy S, failure
Shiu (*Ann Surg*), 1975	297	47	18	55	site, adequacy S
Simon (*J Bone Joint Surg*), 1976	54	54	17	62	site, adequacy S
Enneking (*Cancer*), 1981	40	50	15	?	adequacy S, site, grade
Markhede (*Cancer*), 1982	97	15	22	59	adequacy S, grade
Karakousis (*Cancer*), 1986	53	4	26	63	?
Alho (*Acta Orthop Scand*), 1989	164	23	9	?	adequacy S, size
Rydholm (*J Clin Oncol*), 1991	119	0	11	?	site
Gaynor (*J Clin Oncol*), 1992	387	33	30	46	adequacy S, failure

shown on a series of 649 patients treated at Memorial Hospital that amputation did not improve survival [3]. This is not surprising since patients with locally advanced disease carry a high risk of distant metastases as well.

Conservative approaches have progressively replaced amputation as standard practice. Basically these changes have followed the improvements in reconstructive and plastic surgery: vascular resection followed by prostheses or autologous replacement; synthetic meshes, rotated flaps, for large skin and soft part defects. We will only mention limited resections, such as *marginal and intra capsular resections*, that carry an unacceptable 90–100% risk of long-term local failure. *Radical excision* that aims to take out the entire muscular compartment, while preserving the limb, carries a low failure rate (15–20%). It is made possible by the compartmentalisation of the extremities, which provides natural barriers to tumour extension. It is accompanied by a substantial risk of functional deficit, especially on gait when it removes all quadricipital muscles in the anterior thigh, or sciatic nerve posteriorly, or several leg muscles. In such situations, the patient should preferably be managed with alternative approaches. In some situations, part of muscles can be preserved if it does not compromise safety margins. *Wide excision* (including around 2 cm safety margin) carries about 40% risk by itself, but it can be used in selected situations: small superficial or strictly intra-compartmental lesions, re-excision following a previous intra-lesional resection, and combination with radiotherapy (see section "Timing" under "Radiotherapy" below). In summary, there are consistent data to show that amputation and compartmental excision, when administered alone, provide excellent local control *(level 2)*. Nowadays, despite an increasing use of combined treatment modalities, resection that aims to achieve RO margins should certainly not be disregarded (see Tables 1 and 2).

Radiotherapy [4]

Radiation sensitivity [5]

Conventionally, soft tissue sarcomas have been considered highly radio-resistant tumours that required very high doses of radiation. As mentioned by H.D. Suit, these concepts were established before the advent of megavoltage therapy, at a time when only mild dosages could be administered, and mean tumour volumes were larger due to associated suboptimal imaging and surgical resections. Furthermore,

Table 2
Pre-operative radiotherapy in the management of soft tissue sarcomas in adults (only references mentioned in the text are listed in the reference section)

Author (*journal*), year	No. of patients	Site	% Local failures	% 5-year survival	Comments
Suit (*Cancer*), 1985	90		18	69	–
Lindberg (*Cancer Treat Symp*), 1985	43		7	?	
Sadoski (*J Surg Oncol*), 1993	132		6	68	
Cheng (*J Surg Oncol*), 1996	112	limbs	9–17	75–79	Pre- vs. post-op RT not RO. No difference outcome, pre-op ↑ wound complications
Pollack (*Int J Radiat Oncol Biol Phys*), 1998	128	all	18	?	Biases: gross excision outside institution included, low grade excluded.

the old radiobiological concepts postulated that differentiated and slow-growing populations were more resistant, which are actually common findings in soft tissue sarcomas. These concepts have been revisited in light of modern radiobiology and proven to be incorrect in many instances. As far as soft tissue sarcomas are concerned, experiments conducted at Memorial Hospital in New York, Massachusetts General Hospital, and the University of Chicago have shown that *in vitro*, the fraction of cells that survive a single radiation dose of 2 Gy (SF2), is in the same range as adenocarcinomas of the breast and possibly lower than head and neck squamous cell carcinomas: 44% and 26%, respectively (sarcoma range: 13–54%). Mice experiments display clear correlations between tumour size and local control probability. Tepper and Suit have made clinical correlations between tumour size and total dose as well. They demonstrated that ≥60–65 Gy could control most tumours ≤5 cm. They suggest that TCD 50 (radiation dose that eradicates 50% of the tumour), at 65 ml tumour volume (5 cm across) should be administered at 70–75 Gy, a dose also administered in inoperable small and mid-size carcinomas. On the other hand, radiobiological data indicate a low potential doubling time (in the order of 25 days), along with a high degree of hypoxic tumour cells (at least in non-resectable disease) which makes soft tissue sarcomas good candidates for high linear energy transfer (LET) particles therapy (see below).

Timing

Combined conservative resection and radiotherapy has gained wide acceptance in the management of adult soft tissue sarcomas including high grade ones [6]. The timing of radiotherapy relative to the surgical procedure has also been debated for many years: both pre- and post-operative radiotherapy have support [5].

Pre-operative radiotherapy advantages. The advantages of pre-operative radiotherapy are: (1) rapid control of microscopic extensions; (2) limitation of the dose generally to about 50 Gy and (3) of field sizes (approximately 60% lower), due to the absence of scar, and of contaminated tissues by the surgical procedure; and (4) reduction of the extent of surgical resection (if enough time is allocated to tumour shrinkage). All these advantages translate to an improved sparing of normal tissues and supposedly to a better functional outcome. They also limit the risk of contaminated cell-seeding in the surgical bed and in the vascular spaces. Table 2 summarises outcomes of 5 studies.

Post-operative radiotherapy advantages. The advantages of post-operative radiotherapy are: (1) the pathologist benefits from an "intact" specimen and can assess more accurately tumour grading and safety margins; (2) wound healing is generally faster than when surgery has been administered to an irradiated tissue (especially when tumour is located in the lower limb). Table 3 summarises outcomes of 15 studies.

Which is the best? It should be mentioned that no study comparing pre- and post-operative radiotherapy has come up with any definite superiority of one of them over the other in terms of local control, including a recent Canadian randomised one *(level 1)* [7]. Non-randomised studies are frequently flawed by selection biases in tumour size and grade, as well by different radiotherapeutic parameters such as dose

Table 3

Combined resection and post-operative radiotherapy in adult soft tissue sarcomas (Only references mentioned in the text are listed in the reference section.)

Author (*journal*), year	No. of patients	Site	% Local failures	% 5-year survival	Factors predictive of local failures
Lindberg (*Cancer*), 1981	300	all	22	61	site, size, stage
Wood (*Am J Surg*), 1984	120	all	12	74	?
Karakousis (*Cancer*), 1986	56	all	14	63	?
Mandard (*Cancer*), 1989	80	all except retro perito	31	?	quality resection, necrosis
Robinson (*Radiother Oncol*), 1990	102	limbs	17	55–65	previous failure
Pao (*Int J Radiat Oncol Biol Phys*), 1990	50	limbs	22		post-op gross residue
Avizonis (*J Surg Oncol*), 1990	784	all except retro perito	28	56	previous failure, site
Stotter (*Cancer*), 1990	97	limbs	29	72	gender, quality resection, no RT
Herbert (*Cancer*), 1993	74	limbs	18	70	quality resection, grade
Ravaud (*Br J Cancer*), 1992	141	all	27	66	gender, quality resection
Keus (*Eur J Cancer*), 1994	117	limbs	74–81	69	quality resection, grade, indic RT
Mundt (*Int J Radiat Oncol Biol Phys*), 1995	64	limbs	74–87	76	RT margins and dose
Fein (*Int J Radiat Oncol Biol Phys*), 1995	67	limbs	87	48–80	quality resection, RT dose
Khanfir (in press), 2003	133	limbs	78 (LCFS)	77	quality resection, RT indic

levels. In the Canadian study, a marginal benefit for the pre-operative regimen was shown for survival only. On the other hand, an increased risk of surgical morbidity was shown (see section "Risk factors" under "Functional outcomes" below).

Dose fractionation

Currently, there is a consensus *(level 2)* on recommended doses: about 50 Gy, conventionally fractionated, in large areas at risk for minimally invasive microscopic extension. Boosts where they are indicated should be in the range of 10–15 Gy to the site of primary as defined clinically and radiologically, and possibly an extra dose for gross invasion. There is no clear dose–effect relationship and so no consensus on the indications for a boost: systematic to the primary site for some authors, only in case of microscopic residue, or high grade of the lesion for others *(level 3)*. Despite modern conformal approaches, doses rarely exceed 75 Gy, due to the presence of close critical structures, at least using photons. Most sensitive organs are found in the trunk, and that can make radiotherapeutic management particularly challenging (spinal cord, gut, liver, to mention a few). Most authors recommend a conventionally fractionated administration of the dose, i.e. 1.8–2 Gy, delivered in 5 weekly sessions *(level 2)*. Multifractionation of the dose (i.e. multiple fractions per day) has not been investigated on a large scale, except in paediatric rhabdomyosarcomas (see section "Hyperfractionation" under "Technical innovations" below).

Target volume [4]

The basic principles of modern radiotherapy include the definition of a gross tumour volume (GTV) encompassed by a "safety margin" taking into account microscopic tumour cells extensions which define the clinical target volume (CTV) (Figs. 1 and 2). Strictly speaking, the GTV can only be defined in a pre-operative setting or for inoperable disease. Following surgery, some authors find it convenient to display a putative GTV, based on pre-operative imaging and that includes all tissues handled by the surgeon, i.e. drain sites, scars, synthetic material, and flaps. The CTV corresponds classically to the entire anatomical muscular compartment, limited only laterally by the natural barriers (fascia, bone, etc.). More extensive coverage can be requested by tumours that extend through the fascial planes, the vascular/nervous bundles, or with poor definition of muscular boundaries like those located in the trunk. Due to the enhanced toxicity of extensive target volumes, attempts have been made to restrict this safety margin further: most authors recommend currently

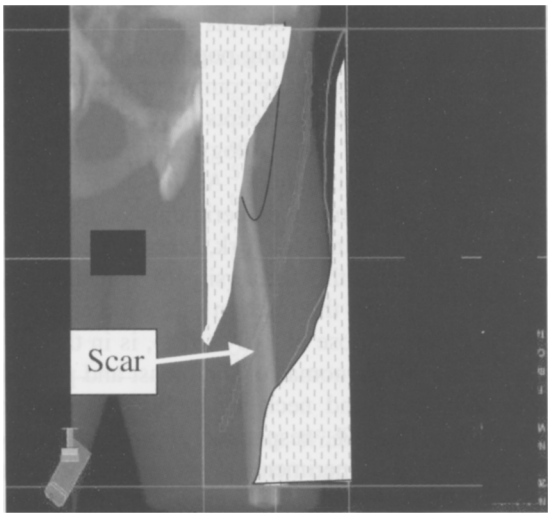

Fig. 1. Spindle cell sarcoma of proximal thigh, in a 44-year-old man. Unplanned excision of a 9.5 cm mass. Re-excision with NED, followed by systematic external radiotherapy. Beam's eye view of CT reconstructed conformal irradiation.

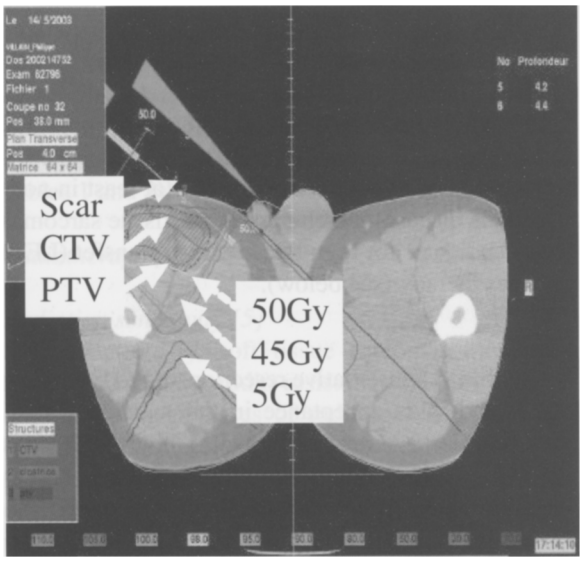

Fig. 2. Same patient as in Fig. 1. Dose distribution in transverse section. Planned dose: 50 Gy. CTV: clinical target volume, PTV: planning target volume.

5–7 cm around the GTV, including any peri-tumoral oedema. Local control in excess of 90% has been reported versus 30% for tighter margins. Margins up to 10 cm have been advocated in cases of high-grade lesions. There is no need for systematic coverage of the lymphatic drainage, due to the rarity of the regional lymphatic involvement (approximately 5%), in adult-type sarcomas. It is still advocated by some authors systematically in histological sub-types that have a higher propensity for lymphatic involvement like alveolar rhabdomyosarcomas or synovial sarcomas.

Chemotherapy, biological agents

Chemotherapy

The role of chemotherapy on the local control of soft tissue sarcoma is unclear, and estimated to be "marginal". Nonetheless, in a recent update of the Sarcoma Meta-Analysis Collaboration (SMAC), it was assessed that the 10% absolute increase in disease-free survival (DFS) at ten years which followed the introduction of anthracycline-based chemotherapy was due to a reduction in both distant metastases and local recurrences (25% vs. 19% on 1315 evaluated cases). Nonetheless, it was recommended to consider these figures cautiously since they could have been obscured by the variety of local treatments applied and tumour sites [8] *(level 2)*. Pre-operative chemotherapy alone or combined with radiotherapy has also been piloted by a few institutions in order to act early on micrometastatic foci and also to render inoperable lesions operable. Following the original publication by Rouesse et al. in our group in the mid-1980s [9], experiences have been reported by UCLA, UC Davis, MD Anderson Hospital, and recently by the Radiation Therapy Oncology Group (RTOG), and the European Organisation for Research and Treatment of Cancer (EORTC). One of the most promising approaches seems the combination of intravenous (i.v.) doxorubicin/platinum/ifosfamide and 28 Gy that yields a 34% complete response rate of the primary [10]. The RTOG report on a modified MAID protocol plus split-course irradiation (total 45 Gy) indicates a 95% 2-year-survival.

Biological agents [8]

These have also emerged recently in the local armamentarium. It has been shown that gastrointestinal stromal tumours (GIST), a newly individualised histopathological entity, express a growth factor receptor with tyrosine kinase activity (c-kit), that could be inhibited by imatinib mesylate, a newly developed tyrosine kinase inhibitor. Promising preliminary experiences of sustained local control in advanced diseases have been brought out [8].

Functional outcome

Results evaluation

Limb-preserving surgery combined with radiotherapy has dramatically improved the functional outcome of patients compared with amputation. But it still carries a substantial risk of acute and long-term side effects. The Toronto group evaluated the function of 88 evaluable patients at two time periods (12 and 24 months) following this approach [11]. The evaluation was based on the Enneking scoring system which ranks from 0 (poor) to 5 (excellent) seven different items (motion, pain, stability, deformity, strength, psychological acceptance, and ability). In 73% of patients, the score was good or excellent (a score of $\geq$21). In 27%, it was fair or poor. This is in agreement with previous studies that found that good or fair results were recorded in the range of 70–80% or so *(level 2)*. In multivariate analysis, tumour size and peri-operative neural sacrifice were significant predictors of the functional outcome in the Canadian study. Poor results took the form of limb weakness due to nerve sacrifices, and fractures, and were mainly seen in proximal thigh and shoulder girdle. As a whole, approximately 50% of the patients resumed full employment. Lower extremity has also been found to be an adverse prognostic indicator by other authors. Reviewing 15 evaluable studies published in the literature until 1999, Davis [12] examined functional outcome under 3 aspects: impairment (such as oedema, fibrosis, etc.), disability (i.e. difficulties performing specific activities), and handicap (i.e. social and professional limitations). Impairments and handicap were observed in 50% or so of patients, but disability was generally much lower, indicating individual compensation in performing activities.

Risk factors

When analysing therapeutic factors, *radiotherapy technique* should not be disregarded. In a study by Stinson et al. [13], joint contracture was predicted by joint inclusion in the radiation field, strength deficit and swelling by size of the fields, and anatomical location in the lower extremity. Several authors have pointed out the deleterious effect of the use of *brachytherapy*, and some others have not. It is our own experience that brachytherapy should be avoided in foot sites that carry a major risk of prolonged radionecrosis. One recent randomised study, conducted by the Canadian group, has also addressed the role of *timing of radiation*, given either pre- or post-operatively [7]. 185 patients with extremity sarcomas were included, and randomised to receive pre- (50 Gy $\pm$ 16–20 Gy post-operatively according to the quality of resection), or post-operative radiotherapy (66 Gy). Patients were scored using objective clinical measurements, and subjective performance evaluations. At 6 weeks post-surgery, patients treated with the post-operative regimen had superior function whatever the scoring scale used *(level 1)*. This difference

subsided progressively until 2 years. Wound complications were more frequent in the pre-operative setting. (35% vs. 17%, $P = 0.01$). Functional outcome was negatively impacted in all groups by tumour characteristics (i.e. large, and located in lower extremities), as well as by surgical characteristics (i.e. with motor nerve sacrifice, prior unplanned excision, and wound complications). Nonetheless, the use of vascularised tissue transfers for wound closure did not seem to improve outcome. Quality of life has rarely been detailed in these studies, and can be compromised despite good functional outcome. Specific items are rarely mentioned and refer to refractory pains, interference between reconstructive procedures and work. Surprisingly, old studies, directed to psycho-social aspects in limbs, evidenced no or few differences between radical and conservative therapies [14]. As far as recent approaches goes, the impact of repeated surgical rehabilitation procedures following wound healing delays has been pointed out.

Treatment strategy

The approach combining conservative resection and radiotherapy has gained wide acceptance in most institutions. It should be combined with a conservative surgical excision as complete as possible. There is no consensus on the extent of surgical clear margins (macro- or only microscopic), but 1–2 cm looks on the "safe" side. Complete resection in patients with low grade, small, superficial lesions can be considered sufficient. In others, radiotherapy is recommended with higher risk of local failure in those with high grade, large primaries (>5 cm), and deep-seated (especially limb girdles and retroperitoneum) tumours. Table 4 summarises randomised studies that have used a combined approach rather than extensive surgery alone (*level 1*). Some of them demonstrate that radiotherapy improves survival as well, but only in high-grade lesions.

Special situations

Retroperitoneal sites

Retroperitoneal sarcomas account for approximately 15% of soft tissue sarcomas. They mostly present as advanced disease and local control remains disappointing. Most authors and recent consensus conferences have pointed out the importance of complete excision *(level 2)* [15]. Resection can be achieved in half of the cases, and, most of the time, at the price of extensive visceral sacrifices including kidney, bowel, spleen or pancreas. Gross resection can be made possible following repeated procedures, but clear margins microscopically are rarely reported. Recent data indicate a long-term survival between 20% and 65%, which is not different from series published over the previous decade. Quality of resection, pathologic grading, tumour size, and tumour status (primary vs. recurrent) represent the most important prognostic factors. The role of conventional radiotherapy given pre- or post-operatively remains controversial *(level 3)*. There has also been a considerable interest in intra-operative radiotherapy (IORT) using electrons, or brachytherapy, especially in the US, with marginal benefits reported. It is interesting to notice that in-field failures seem rare following IORT. Toxicity appears substantial, especially when brachytherapy is directed to the upper abdomen. There is only one randomised study [16] that compared the administration of an intra-operative electron boost (15 Gy) to no boost, following a course of external beam (35 Gy) in grossly-resected sarcomas. Although it shows a significant benefit on local control (but not on survival), from the addition of intra-operative electrons to external beam, the num-

Table 4
Phase III randomised trials on the role of external beam radiotherapy in the local management of soft tissue sarcomas in adults (only references mentioned in the text are listed in the reference section)

Author (*journal*), year	No. of patients	Site	Trial design	% Local failures	Comments
Rosenberg (*Ann Surg*), 1982	43	limbs	amputation vs. conserv S + ERT (± CT)	0 vs. 15	Borderline advantage on local control, none on S.
Sindelar (*Arch Surg*), 1993	35	retro peritoneal	IORT + ERT vs. ERT alone	40 vs. 80	Small trial, no S advantage. Nervous toxicity with IORT.
Yang (*J Clin Oncol*), 1998	141	limbs	conserv S RO ± ERT ± CT (high grade)	20/33 vs. 0/4 (lg/hg)	Significant effect local control, no effect S.
O'Sullivan (*Proc Int J Radiat Oncol Biol Phys*), 2001; (*Lancet*), 2002	190	limbs	pre- vs. post-op ERT	7 vs. 7	Positive impact pre-op on S, but ↑ wound toxicity.

ber of patients included (35) does not allow any firm conclusion *(level 2)*. It should be mentioned that toxicity of this technique appears quite low, except for neurological complications, when inclusion of peripheral nerves cannot be avoided.

Desmoid tumours [17]

Presentation

Also called aggressive fibromatosis or well-differentiated fibromatosis, these rare conditions (approximately 3.5% of fibrous tissue neoplasms, and $\leq$0.1% of all solid tumours) are true neoplastic lesions with proliferation of connective tissue, but no cytological features of malignancy. Multifocal sites within the same muscular compartment have been reported as well and should be looked for by MRI study. Adverse prognostic factors are large tumour size, young age at presentation, positive margins at surgery, and abdominal site.

Management

Due to their rarity, there is no consensus on their optimal management. The primary goal for treatment is gross total resection, advocated by most authors *(level 2)*. This can be achieved in only two-thirds of cases, due to their infiltrative nature, especially in abdominal locations. Patients with complete resection microscopically of a primary lesion can expect 80% chances of local control, and only 33–60%, if margins are positive. The role of radiotherapy is controversial *(level 3)*, but generally put forward in patients at a high risk of local failure (i.e. positive margins on the surgical specimen, local recurrence). Local control is about 80% using combined modalities. Optimal doses seem to range between 50 Gy and 60 Gy, with higher doses suitable for non-resectable lesions.

Unplanned excision [18]

In cancer centres, about half of sarcoma patients are seen following a limited resection or an enucleation done elsewhere with no peripheral safety margin and no documented pre-operative imaging. The main reason is that the diagnosis was initially disregarded. Approximately half of them have no evidence of residual disease, both on physical examination and on imaging. The usual policy is to make a wide re-excision of the "scar", along with a frozen section, in order to secure safe margins. In the Toronto experience [18], more than one-third of these systematic procedures confirm the presence of residual disease, and inadequate margins in 40% of them. Indications for more extensive surgery and adjuvant therapy follow guidelines similar to those of patients treated upfront.

Primary site failure

Work-up

Approximately 20% of limb sarcomas and over 40% of retroperitoneal sites will recur locally, most within 2 years. Salvage management is a complex process that requires an extensive evaluation of the local failure (based on physical examination, detailed imaging including CT scan in intra-abdominal sites and MRI in extremities), a metastatic work-up (CT scan of the chest $\pm$ oriented tests), and a full review of previous therapy, especially radiotherapeutic technical data.

Management [19]

It is controversial to say so, but it obviously makes a difference whether the patient has been irradiated previously or not. In the latter situation, a conservative management combining surgical excision and radiotherapy can be recommended with a long-term local control close to that of non-recurrent tumours. A possible exception is a small (<5 cm), superficial low-grade recurrence of the extremities that can be approached with surgery alone. In the former situation, amputation remains standard practice in extremity lesions *(level 2)*. An experimental alternative to amputation is a limb perfusion followed by conservative surgery that yielded 80% limb salvage in a review of mixed recurrent and non-recurrent tumours. Re-irradiation administering full dose with external beam or brachytherapy has also been tested at the price of a substantial toxicity. This is particularly sensitive in retroperitoneal sites where some authors have advocated intra-operative electrons, in order to maximise the sparing of critical anatomical sites.

Unresectable tumours [4]

This is a rare situation, with very limited literature available. It can be encountered when a large lesion encircles major vascular structures at the limbs girdles. High-dose radiation ($\geq$65 Gy) is advisable although long-term local control is observed in only approximately 1/3 of cases. The use of heavy particles has been tested on limited series, with promising results (see section "Neutron therapy" under "Technical advances" below). Similarly, the isolated limb perfusion has provided dramatic tumour-response in limited series (see section "Isolated limb perfusion" under "Technical advances" below). There are also technical constraints, such as the necessity to posi-

tion an arterial tourniquet upstream, that can limit its feasibility.

Technical advances

Isolated limb perfusion

Indications

This technique was first described to treat melanoma in-transit metastases in the extremities. It was shown that regional cytostatic concentrations are 15–20 times higher than those achieved during i.v. infusion, and systemic toxicity was minimal. In soft tissue sarcomas, the rationale was to try to render large extremity primaries amenable to conservative surgery. Tumours indicated for this approach are extensive ones requiring extensive muscular and/or nervous sacrifice, and those located close to vital structures such as a major artery.

Technique

First attempts to infuse cytostatic drugs such as Melphalan have been disappointing. More recently, Lejeune and Lienard, and Eggermont have investigated the combination of tumour necrotising factor (TNF) and Melphalan, associated or not with interferon-γ (IFN) in phases II studies [20] (*level 3*). IFN and TNF were injected as successive boluses into the arterial line, under mild hyperthermia (39–40°C).

Results

In the Eggermont series (125 patients), about 30% of patients obtained complete pathologic remission, 50% partial remission, and 15% stable disease [20]. Limb preservation was recorded in over 80% at two years. It was followed by radiotherapy if margins were close or positive. Severe regional toxicity leading to an amputation was very rare. 5% of patients also presented with long-lasting paraesthesia in the treated limb. Radiotherapy was well tolerated except in those with grade 4–5 post-infusion toxicity. A similar experience has been reported for 34 patients by Olieman et al. [21]. Interestingly, only the subgroup with positive margins that received radiotherapy (60 Gy) did not fail locally, against 26% for those with negative margins who were not irradiated.

Brachytherapy [4]

Rationale

This is the preferred radiotherapeutic option in most institutions with a large experience in this field. Its results are summarised in Table 5. Its advantages are two-fold: (1) Physical due to a rapid fall-off of the dose beyond the target volume; and tighter safety margins compared with external beam therapy (avoiding margins for set-up uncertainties); (2) Clinical since it allows precise intra-operative mapping of the area at risks for dissemination, and does not interfere with wound healing due to delayed acute reactions (differing by 3 weeks or more).

Technique

Low dose rate (LDR) has been the traditional mode of administration and presents further biological advantages: repair of sub-lethal injuries to normal tissues without compromising tumour cell killing; improved efficacy on hypoxic tumour cells; and reduction of overall treatment time that prevents

Table 5
Brachytherapy in the management of soft tissue sarcomas (only references mentioned in the text are listed in the reference section)

Author (*journal*), year	No. of patients	Site	Design	% Local failures	Comments
Shiu (*Cancer*), 1984	33	limbs	conservative S + BT	0–37	Advanced cases, better local control in previously untreated.
Habrand (*Int J Radiat Oncol Biol Phys*), 1991	50	limbs + trunk + hand N	conserv S + BT ± ERT	35	Trunkal site and BT for failure correlated with outcome.
Chaudhary (*Strahlenther Onkol*), 1998	151			29	
Pisters (*J Clin Oncol*), 1996	119	extremities + trunk	S RO ± BT	18–31	Significant advantage BT in high grade only. No influence S.
Schray (*Cancer*), 1990	63	all except retro perito	conserv S + BT ± ERT	4	
Gemer (*Int J Radiat Oncol Biol Phys*), 1991	25		conserv S + BT ± ERT	20	Effect dose <65 Gy on local failure.
Delannes (*Int J Radiat Oncol Biol Phys*), 2000	58	extremities + trunk	conserv S + BT + ERT	11	Limb site correlated with acute toxicity, and vicinity neurovascular structures late one.
Rosenblatt (*Sarcoma*), 1999	25			6	

tumour-clonogen repopulation. The usual technique consists in the implantation of parallel interstitial catheters placed in a single plane (given there is no gross residual disease present), sometimes woven in flexible applicators, and distant by 1–1.5 cm. Tubes are after-loaded using ^{192}Iridium. Permanent ^{125}Iodine seeds are less widely available and there is no reported experience with them in sarcomas. High dose rate (HDR) techniques present practical advantages such as improved radiation safety, outpatient management and lower costs.

Indications and results

There are very limited data available in the management of soft tissue sarcomas. Moreover, there are still uncertainties about the optimal dose fractionation based on HDR that makes the management of patients (such as children) with close sensitive structures hazardous. One randomised series is available using LDR, showing a marked advantage compared with those not receiving it. Non-randomised series show a long-term local control rate between 65% and 90%. Small pilot series dealing with HDR suggest an outcome close to that of LDR. Recently the American Brachytherapy Society provided an expert consensus on its actual place [22] *(level 2)*: (1) Brachytherapy can be used in intermediate- to high-grade sarcomas as a boost to wide-field external beam if margins are positive or negative. The technique is not validated in low-grade sarcomas, but published series are too small to draw firm conclusions on its role. (2) Brachytherapy can be used as a single modality in superficial trunk or limbs with negative surgical margins.

Hyperthermia

Rationale and technical aspects

Hyperthermia, a therapy described by the Egyptians in a surgical papyrus, was rediscovered in the late 19th century and has been extensively tested in cancer since the mid-1970s. Its rationale is based on the well-known cytotoxic effects of temperatures exceeding 40–42°C. Moreover, it has been shown to act on the cellular microenvironment, especially microvasculature, to improve tumour oxygenation and possibly at a genetic level, to alter gene expression. One salient feature in clinical practice is the potentiation of ionising radiation effects, that has made combinations of hyperthermia and low-dose radiation attractive in local failures in previously irradiated areas. A major technical limitation has been the difficulty to maintain a high degree of temperature for an hour or so, especially in deep-seated locations, due to the efficient cooling effect of the blood flow. Recent equipments overcome most of these difficulties, and promising results have been observed in pelvic tumours.

Clinical aspects

As for soft tissue sarcomas, three pilot studies with over 200 patients have recently looked at locally advanced or recurrent tumours *(level 3)*. In the first study [23], hyperthermia (2 sessions per week) was combined with radiotherapy pre-operatively in large high-grade lesions, mainly located in the extremities. A conservative resection was planned 4–6 weeks later. With a median follow-up of 32 months, only 2 patients experienced local progression. Nonetheless, 10-year overall survival (50%) did not seem to be positively influenced. Hyperthermia complications were mild and did not interfere with the treatment programme. In the two other studies [24], patients received an initial chemotherapy regimen (etoposide, ifosfamide, doxorubicin), followed by surgical resection, post-operative chemotherapy and external beam radiation, except in recurrent tumours previously irradiated. Hyperthermia was combined with the administration of pre-operative chemotherapy and in half of them with a post-operative one as well. Local failure-free survival was 40% in those receiving the entire programme and not as good when post-operative hyperthermia was omitted. Five-year survival was close to 50% in both approaches. The EORTC–STBSG is currently conducting a phase III multicentre trial in advanced non-curable presentations. Patients are allocated to receive upfront either 4 cycles of EIA regimen (etoposide, efosfamide, and doxorubicin), or EIA combined with hyperthermia and followed by local treatment. Over 150 patients have been included in this study [25].

Neutron therapy

Biological properties

Fast neutrons are high LET particles that offer specific biological advantages over photons: better ability to kill hypoxic cells (induced by direct lethal damages not mediated by oxygen); to induce non-reparable cell-damages (due to a larger amount of energy deposited in small critical targets such as DNA); to kill cells in "radio-resistant" phases of the cell-cycle (especially the "S" phase); and to act on slowly proliferating cells (related to reduced slow-repair mechanisms, known as PLDR). These purely biological advantages (there is no substantial ballistic advantages of neutrons over photons) make these particles theoretically suitable in the management of hy-

poxic, "radio-resistant", slowly proliferating malignancies. As far as soft tissue sarcomas are concerned, it should also be mentioned that neutron energy deposition seems superior in soft tissues than in bones.

Clinical applications

Whether these properties have relevance to any given clinical situation depends on the cycling properties of the tumour compared with that of the normal tissues included in the treated volume. It has also been conditioned in early experiments by beam quality, since most neutron sources had poor depth-dose characteristics. Actually the trade-off between efficacy and toxicity has been critical in most clinical studies dealing with neutrons. It is noteworthy that none of multiple randomised studies conducted by the RTOG has evidenced clear superiority of neutrons over photons in various tumour sites [26,27]. *(level 1)*. Nonetheless, locally very advanced sarcomas (especially if they are low-grade), which have $\leq$30–35% disease-free survival using photons alone, can be considered for this technique. Long-term local control in the literature approximates 50% (range 20–70%). There is also a growing interest for "heavy ions", especially carbon ions, which are currently under investigations in Japan and Germany. These particles combine the biological advantages of neutrons and the ballistic selectivity of protons. Early experiments indicate that they can be used safely and effectively in advanced cases.

PAEDIATRIC: Treatment modalities in paediatric soft tissue sarcomas

Surgery

Its historical place

This was the unique treatment, until the advent of new treatment modalities. Unfortunately, due to the high propensity of the most common histological types to metastasise early, surgery was able to cure less than 10% of cases in children. Nowadays, surgical excision is very rarely performed as a single treatment modality, and, instead, is combined with chemotherapy and radiotherapy. In most cases, extensive resections are no longer advocated, with a few exceptions (refractory disease and local failures).

Its current place

Its exact place remains controversial and can differ on either side of the Atlantic. In RMS, the most common histological variant, it is generally part of a multimodal strategy. In non-RMS sarcomas, the place of surgical resection can be predominant.

US approach. The Intergroup Rhabdomyosarcoma Study (IRS) group still considers initial surgery as a cornerstone in the management which conditions patients' staging and outcome.

European approach. For the International Society of Paediatric Oncology (SIOP), the therapeutic strategy is based on a clinical staging, including modern imaging, and surgical resection upfront is only recommended in small, readily accessible lesions. Delayed surgical resection following a prolonged course of chemotherapy is not systematic, but is applied to minimal gross residue.

Radiotherapy

Radiation sensitivity

A substantial number of clinical and radiobiological experiments show that RMS presents with a remarkable sensitivity. Early experiments conducted in orbital RMS showed that radiation to a dose of approximately 50 Gy given alone could control virtually all patients locally. Kelland [28], using a human RMS cell line (HX 170c), found an SF 2 of 26%. Using also a continuous LDR of 3.2 cGy/min (similar to that used in brachytherapy), he showed very low repair capacities, as evidenced by negligible "shoulders" in the initial portion of the survival curve. In the R1H murine model, tumour oxygenation has been shown to remain constant up to doses of approximately 45 Gy, but to progressively decrease above that level, possibly due to vascular damages. Hyperfractionation of the dose using doses $\leq$1 Gy seems more efficient experimentally than conventional fractionation.

Dose fractionation

There is no consensus on the radiation dosages that are necessary to cure RMS, especially when gross tumour is present *(level 3)*. Doses in the range of 40–55 Gy, 1.8–2.0 Gy, 5 days/week, depending on the tumour burden at the time of radiation, have been recommended in the IRS studies. They are typically age- and size-adapted when gross disease is present, like in the IRS III study [29]: 40–45 Gy if $<$6 years of age, and $<$5 cm; 45–50 Gy if $<$6 years of age and $>$5 cm, or if $>$6 years of age and $<$5 cm; 50–55 Gy if $>$6 years of age and $>$5 cm. This tailor-fit policy has contributed to obscure somewhat the optimal dose fractionation. There are several mono-institutional studies indicating that 40 Gy is safe when microscopic disease is present (pathological group II) following chemotherapy and/or surgical resection. Doses down to 32 Gy have been tested by the

German group with accelerated-hyperfractionation, but on small subsets of patients. The IRS group is currently testing 36 Gy in cases of microscopic residual following surgery. In Europe, SIOP studies have applied a rather uniform dose range of 45–50 Gy given in 5 weekly sessions of 1.5–2 Gy, depending on the treated volume, and the presence or not of critical structures such as the small bowel.

Target volume

This is also controversial *(level 3)* except in parameningeal sites *(level 2)*. IRS I recommended encompassing the entire muscle bundle. However, a quality review showed that children "inadequately" treated in the initial tumour volume + 5 cm safety margin fared as well as those treated "adequately" in the entire compartment. Since then, most studies have recommended an initial tumour volume coverage of + 3–4 cm safety margin (2 cm in head and neck sites). Nonetheless, SIOP, following an early randomised trial (MMT 75), has elected to cover the residual disease following a prolonged course of chemotherapy: there was no difference in DFS whether the initial or the residual tumour volume was encompassed. It should be mentioned that the number of patients was small, local treatment a mixture of surgical resection and radiotherapy, and follow-up limited [30].

Indications for radiotherapy in the US

Group I. Group I (i.e. initial complete surgical resection) with a favourable histology (i.e. embryonal /botryoid): Keep away from systematic radiotherapy. This is based on IRS I randomised trial *(level 1)*. This rather small subset of patients (about 100 patients, 15% of the population), was elected to receive radiotherapy or not [31]. All received the VAC (vincristine, actinomycin D, cyclophosphamide) regimen concomitantly. Five-year DFS was about 80% and 5-year survival was in excess of 80% in both groups. These excellent results have been confirmed in the subsequent IRS studies (5-year DFS $\geq$80% in IRS II, III, and IV) in a non-randomised manner, but on a larger population-scale (two-fold in IRS III), along with a reduction in chemotherapy intensity. It is noteworthy that in less favourable group I patients (i.e. alveolar/undifferentiated histologies), the use of RT still improves DFS and survival as evidenced by pooled data from IRS I and II *(level 2)*.

Group II. Group II patients (resectable, with microscopic residual disease), a larger group that represents approximately a quarter of the population: All IRS studies have recommended the systematic use of radiotherapy with also quite a good outcome (DFS: 65–75%, and S: 70–90%, from IRS I to III) *(level 2)*. Local control *per se* seems to be in the order of 90% in limited but more detailed analyses.

Group III. Group III (grossly unresectable disease) patients is the largest population (approximately 40%), but also the most difficult to control: 39–87% local control (Table 6). An IRS II analysis by Wharam showed that patients at higher risk were those with sites located below the clavicle (i.e. trunk, extremities), and those with tumours >10 cm. The need for improvement has stimulated interest in this stage group for technical innovations, mainly altered fractionations, combined with CT (see section "Hyperfractionation" under "Technical innovations" below). It should also be mentioned that radiotherapy is initiated early in the treatment course (generally week 0–6 depending on tumour stage and site).

Table 6

Local control with radiotherapy, in childhood rhabdomyosarcomas with no or sub-total resections (only references mentioned in the text are listed in the reference section)

Author (*journal*), year	No. of patients	% Local control	Comments
Jereb (*Int J Radiat Oncol Biol Phys*), 1980	41	63	
Tefft (*Natl Cancer Inst Monogr*), 1981	352	87	
Wharam (*Int J Radiat Oncol Biol Phys*), 1997	362	74–86	Increased risk if >10 cm or site below clavicle
Kun (*Proc Int J Radiat Oncol Biol Phys*), 1986	49	39	
Etcubanas (*Arch Surg*), 1987	22	60	
Mandell (*Int J Radiat Oncol Biol Phys*), 1988	12	83	Split course accelerated RT
Koscielniak (*Cancer*), 1992	61	79	
Mameghan (*Med Pediatr Oncol*), 1993	29	69	
Regine (*Int J Radiat Oncol Biol Phys*), 1995	25	86	Part received accelerated RT
Habrand (*Proc Int J Radiat Oncol Biol Phys*), 1997	308	86	Small subgroups received accelerated RT, or brachytherapy
Koscielniak (*J Clin Oncol*), 1999	116	78–87	RT dose effect on local control
Donaldson (*Int J Radiat Oncol Biol Phys*), 2001	490	84	Randomised between hyperfractionated and conventional: no statistical difference

Indications for radiotherapy in Europe

Since 1984 (MMT-84 study), radiotherapy has been confined to "high risk" patients, i.e. those with para-meningeal sites, with residual disease following an initial course of chemotherapy completed or not with surgical resection, and of course to patients who fail following an initial regimen that did not include radiotherapy [32]. In the MMT-89 study, which ran between 1989 and 1995, radiotherapy was requested in 84% of para-meningeal, but only 17% of genito-urinary sites (unpublished data). Although directed to unfavourable cases, 5-year survival and disease-free survival of irradiated children was 66% and 60%, respectively, versus 72% and 58% for the entire population.

Complications and long-term sequelae of therapy

Predisposing factors

Many factors contribute to the deleterious effects of therapy in children affected by soft tissue sarcomas:

These tumours can affect very young children, who have an exquisite sensitivity to radiations (especially for growing plates, and CNS).

They arise in virtually any body site.

Management for the past three decades has combined chemotherapy, radiotherapy and surgery in most patients. Each carries its own toxicity and toxic interactions are possible (for example, the combination of radiations and actinomycin D or anthracyclines). As far as radiotherapy goes, high doses are frequently requested along with extensive target volumes due to local invasiveness.

Paradigm of head and neck sites

Head and neck sites represent 40% of cases and are particularly challenging. The IRS group has reported 77% late side effects in extra-orbital sites [33]. This included 48% growth disturbances due to primary interaction of radiations with growing cartilages and to pituitary failure, but also frequent cosmetic deformities, poor dentition, decreased vision (due to cataract formation or optic atrophy), hearing impairments, and second malignancies (approximately 1% of cases). Other authors have pointed out the role of high dose radiation and of actinomycin D in the genesis of second neoplasms. Quality of life currently represents a major endpoint in the evaluation of all treatment strategies. This implies the design of multimodal treatments that minimise the intensity of each agent given alone, and avoid interactive agents, and also the implementation of technical innovations such as brachytherapy, altered fractionations, and conformal irradiation (see "Technical innovations" below).

Treatment strategies and outcome

As mentioned above, there are large variations in the therapeutic approaches on both sides of the Atlantic.

American approach

Surgical resection completed with radiotherapy remains the mainstay of therapy, except in highly favourable situations. Chemotherapy acts as an adjuvant treatment that aims to limit distant dissemination. IRS benefits from the largest world experience.

European approach

Children with favourable features receive chemotherapy as a single modality, whereas those with more aggressive factors still receive radiotherapy combined or not with surgical resection.

Which is best?

Recent updates indicate that the US approach brings a slight survival benefit, and, more remarkably, a superior disease-free survival. All in all, 60–70% of children can be cured using modern strategies, with considerable improvements in long-term side effects.

Special situations

Para-meningeal sites [34]

These represent very common sites of paediatric sarcomas: 15% of the IRS population and 40% of head and neck locations. Two-thirds of the children are below 9 years of age and very young children are also seen. They have in common their anatomical situation across the skull base that carries a potential risk for intra-cranial extension and lepto-meningeal seeding in approximately one-third of cases. Although specific meningitis is uncommon initially, patients frequently present with intra-cranial masses, associated with cranial-nerve palsies. Site of the primary lies in the infra-temporal fossa, middle ear, nasal cavity and para-nasal sinuses (Fig. 3). Para-meningeal sites traditionally carry a poor prognosis. One reason is that

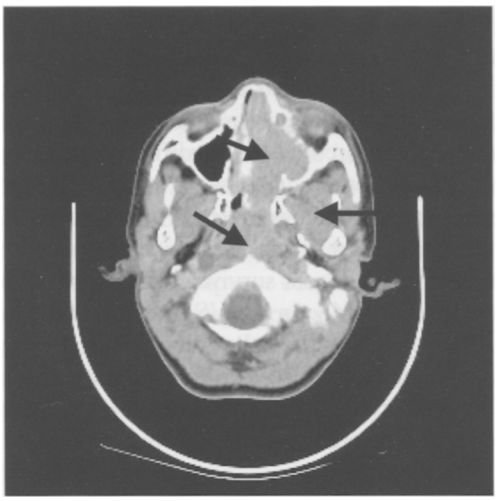

Fig. 3. Para-meningeal alveolar rhabdomyosarcoma in an 8-year old boy with cervical nodal invasion. Initial CT scan shows massive infiltration of para-nasal sinuses.

these sites are deemed not very amenable to surgical resection. Another reason in the past was the frequent underestimation of their exact extension, especially towards the skull base, and so the target volume coverage was inadequate. Improvements were made in the mid-1980s when full cranial inclusion (and even CNS coverage for CSF-positive children) was recommended in the international studies. A better knowledge of areas at risk has followed the introduction of CT scans and, more recently, MRI. This has paralleled further improvements in their outcome and allowed the use of more restricted volumes, such as the primary site along with the base of skull only, when the CSF was negative (Fig. 4). Recently, conformal therapy, based on a 3-D virtual simulation, has been advocated with no clinical evaluation so far. Systematic use of radiation early in the course of the disease, with fair compliance to quality programmes, has shifted the 5-year survival to around 70%.

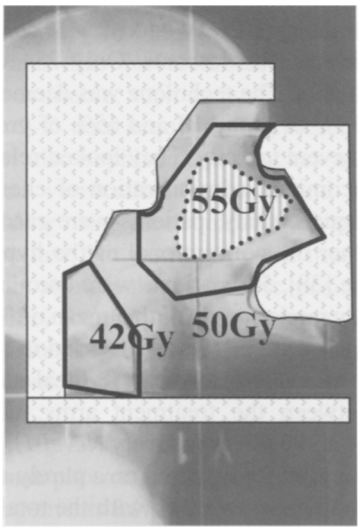

Fig. 4. Same patient as in Fig. 3. Simulation film. Planned dose: 55 Gy to GTV (shaded area), through 2 opposed laterals + 1 anterior supra clavicular. Cone-down at 42 Gy and 50 Gy.

Genito-urinary sites [35]

Therapeutic strategy

These comprise a variety of sites that behave differently, and require different managements. Altogether they represent 25% of the paediatric population. With the introduction of multi-modal therapy which combines chemotherapy, radiotherapy, and surgery, the local control and functional outcome have dramatically improved. Extensive surgery such as total cystectomy, total hysterectomy, pelvic exenteration, should give way to conservative approaches as much as possible.

Bladder and prostate

They arise generally in males below the age of 5 years. One-third of patients have been reported to carry a lymphatic involvement. Initial chemotherapy has become a standard approach that induces dramatic tumour shrinkage in the vast majority of children and allows organ-preserving surgery. In IRS, an intensive chemotherapy regimen combining vincristine, actinomycin D, doxorubicin, cisplatin, VP-16 more than doubled the bladder salvage rate, which was shifted from 25% to 60%. Radiotherapy remains necessary in cases of incomplete or "unclear" resection microscopically. In this setting, brachytherapy can play a major role.

Para-testicular

RMS represents the most common neoplastic cause of scrotal mass in children until 7 years of age, but is more common in older children. It frequently spreads through the lymphatics to the para-aortic nodes at the level of the renal hilar. Pathologically-assessed lymphatic involvement occurs in a quarter of patients in IRS. The value of CT scan in predicting nodal involvement is not firmly demonstrated, so IRS is still recommending lymph node sampling in the pelvis and abdomen, except in group I patients. SIOP favours chemotherapy alone in order to eradicate microscopic lymphatic involvement. As far as the primary is concerned, an orchiectomy is performed through an inguinal incision with high ligation of the spermatic cord. Radiotherapy is administered if the nodes or tumour margins are positive (ipsi-lateral iliac and peri-aortic drainage). The hemiscrotum can be irradiated if there is gross or microscopic residue (sometimes

at the price of a testicular transposition), but hemiscrotectomy remains the preferred option. Five-year survival and DFS are in excess of 80% in the recent IRS/SIOP studies, although somewhat lower if the primary >5 cm, and if the patient is >10 years of age.

Gynaecological sites

They affect preferentially the vagina, but also the vulva, cervix and corpus uteri. They are frequently diagnosed below the age of three years. An initial chemotherapy regimen allows a conservative local treatment in most cases. Our group favours the administration of LDR brachytherapy, using intracavitary acrylic moulds, as exclusive local treatment. This is associated with an ovarian transposition in order to keep the ovaries away from the high dose volume. In 38 girls treated with an initial CT, overall survival was 91%. Local therapy could be conservative in eight, and even though it was unnecessary, in 13, with complete remission. Similarly, the American group has increasingly stopped using hysterectomy in this age group (from 48% in IRS I/II down to 22% in IRS III/IV).

Orbital

Orbital RMSs represent 10% of the entire population. They carry a favourable prognosis with a 5-year survival in excess of 85%. Radiotherapy represents the mainstay of treatment for most authors, although significant long-term sequelae have been associated with it. The IRS group has reported 72% dry eyes, 54% impaired vision, 51% cataracts, 36% ptosis, and 29% orbital hypoplasia. For these reasons, SIOP has explored alternative approaches (see treatment strategies), based mainly on chemotherapy. A recent international workshop compared tumour and functional outcome following different approaches in the US and in Europe, in 306 evaluable children, treated between 1979 and 1992. Only 37% of the SIOP patients received radiotherapy, unlike those included in other studies (70% to 93%, irradiated). As expected, local failures were more common in the non-irradiated children (44% vs. 8%). But interestingly, the 10-year overall survival was strictly superimposable for both therapeutic approaches (86%), which indicates that salvage of non-irradiated children could be quite satisfactory. A non-matched analysis of long-term side effects was clearly in favour of the SIOP policy [36].

Non-RMS soft tissue sarcomas [37]

This is a heterogeneous group whose management is not univocal. SIOP has made recommendations according to the supposed chemosensitivity: high (primitive neuroectodermal tumours, extra osseous Ewing's, undifferentiated and embryonal sarcomas); moderate (synovial sarcomas, malignant fibrous histiocytomas, fibrosarcoma, and undifferentiated liposarcoma) or low (other subtypes). The first two groups receive a treatment close to RMS, with selective local treatment. The last group is managed primarily with local therapy. Five-year survival and DFS seem in the same range as RMS. In the US, the Pediatric Oncology Group has explored the role of radiotherapy on these tumour types. The local control rate of groups I, II, and selected III was in excess of 90% except in large lesions where it was inferior by 10 points.

Technical innovations

Hyperfractionation

Rationale

Some data suggest that doses above 55 Gy could improve local control, but at the price of severe toxicity. Animal models such as weanling rats have been used to demonstrate improved sparing of growing structures using hyperfractionation of the dose. Such models have helped to design new studies based on altered fractionations. The IRS tested in group III and IV, a dose increment up to 59.4 Gy administered in 2 daily fractions of 1.1 Gy each. According to the linear quadratic model, it was supposed to increase cell killing by 10% to 20% relative to conventional doses, without altering substantially normal tissue tolerance.

Clinical investigations

A preliminary IRS IV study was conducted on 449 children and adolescents. Only 284 were eventually evaluable. The technique was deemed feasible, although 75% of group III and 65% of group IV experienced severe toxicity. They looked related in part to the concomitant administration of chemotherapy. In a subsequent study, patients were randomised to receive either the conventional or the hyperfractionated regime [38]. 559 patients were enrolled but only 490 actually randomised. With a mean of 3.9 years of follow-up, no difference was recorded in terms of 5-year survival, event-free survival, local and regional failures between the treatment arms: about 77%, 73%, 13%, and 5%, respectively *(level 1)*. SIOP also conducted a pilot study, based on a purely accelerated regimen (1.5 Gy given BID), with the total dose kept constant (about 45 Gy) and similar findings.

Brachytherapy

Indications

The use of brachytherapy in children is an attractive alternative to external beam irradiation since it irradiates small volumes and potentially minimises complications. It can be used alone to treat small residual tumours following an initial course of cytoreductive chemotherapy, or combined with external beam irradiation to larger primaries. The first approach is particularly indicated in very young children, in order to maximise the sparing of normal anatomical structures.

Technique and outcome

Miniaturised radio nuclides, such as ^{192}Iridium or ^{125}Iodine, are particularly well-adapted to the reduced target and anatomical structures seen in young children. Widespread anatomical sites are accessible to this technique, although bladder-prostate and gynaecological tract have been particularly successful. LDR should represent the standard and HDR [15] should be considered experimental since it carries potentially more toxicity. Current clinical experience remains limited to only a few centres with high expertise, but suggests that in selected cases, local control is in the order of 65–90%, and toxicity <30% [22,39] *(level 2).*

Conformal external radiotherapy

Rationale

This is a newly introduced concept that appears highly attractive in terms of improved dosimetric target coverage, and the sparing of adjacent critical structures. It still calls for clinical validation in this area, and also for technical refinements, still not widely available, such as powerful 3-D software that allows 3-D data acquisition, representation, and calculation; also sophisticated couches and gantries with on-line verification imaging, and customised beam shielding using electronically-driven multi-leaf collimators; last, but not least, rigid immobilisation devices that allow sub-centimetric positioning and reproducibility for the entire treatment course. Parameningeal sites represent typical paradigms of the use of 3D-conformal approaches.

Techniques

Conformal photon techniques based on multiple beam arrangements have been improved with the introduction of non-coplanar approaches, and recently with beam intensity modulation that allows an elegant sparing of critical structures such as the parotid glands in head and neck carcinomas. An evaluation in sarcomas is still missing. In ballistically challenging situations, in which a sub-millimetric positioning is requested (due to close contacts between tumour and eyes or spinal cord, for example), the use of accelerated protons can be helpful.

Conclusions

Soft tissue sarcomas are rare tumours with polymorphic presentations, both in childhood and adulthood. Their local management needs to be by a multidisciplinary team of cancer specialists experienced in these fields. The radical surgical procedures of the past have given way to combined modality approaches in which pre- or post-operative radiotherapy plays an important role. Chemotherapy also plays a significant role in the paediatric types, especially in sites critical for functional preservation such as the bladder, vagina, and orbit. Radiotherapeutic innovations are frequently called for when high doses are administered, and when sensitive normal structures (especially in the abdomen and in children) are concerned. They include 3-D conformal external beam radiotherapy, brachytherapy, intra-operative electrons, and sometimes hyperthermia, intra-arterial infusions of chemotherapeutic agents, and fast neutrons. In the future, it is likely that ballistic innovations, like intensity modulation and protons, as well as biological markers and biological agents, will help to refine local treatment further.

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