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INTRODUCTION

RECENT REPORTS of multicentre studies on the application of isolated limb perfusion with tumour necrosis factor-α (TNFα) and Melphalan in the management of irresectable and borderline resectable locally advanced soft tissue sarcomas of the extremities, as a method of avoiding amputations and achieving limb salvage with preservation of as much function as is attainable, has renewed the discussion about the limits of applying limb-sparing strategies, the benefits and the potential risks [1, 2].

Results of primary surgical treatment of soft tissue sarcomas of the extremities are hampered by the often large size of these tumours at presentation. In extremities, local failure rates of 35% and high amputation rates up to 50% were not unusual in the recent past [3]. Tumour grade, tumour size and deep location are the three most important prognostic factors for disease-specific survival: deep-seated grade 3 tumours (high grade), greater than 5 cm in size, have a greater than 60% failure rate [4]. Further unfavourable prognostic factors in localised extremity sarcoma are positive margins, local recurrence at presentation and tumours situated in the lower extremity [5].

LOCAL CONTROL IS NOT AN INDEPENDENT PROGNOSTIC VARIABLE IN EXTREMITY SOFT TISSUE SARCOMA. AMPUTATIONS DO NOT IMPROVE SURVIVAL

In contrast to one study reporting improved local control to correlate with better survival [6], several studies have shown that local control is not an independent prognostic factor in extremity soft tissue sarcoma. Amputations do not improve survival rates in patients with large (> 5 cm), deep-seated, high-grade sarcomas [7], while other studies have reported similar conclusions on the lack of impact of local recurrences on survival [8–10]. In a small randomised trial comparing amputation versus marginal excision followed by radiation therapy, a higher local recurrence rate was observed in the resection + radiation therapy arm of the study but survival was the same in both arms [11]. Similarly, the experience in a randomised trial at the Memorial Sloan-Kettering Institute demonstrated that limb-sparing marginal resections followed by adjuvant radiation delivered as brachytherapy markedly reduced the rate of local recurrences but survival was not affected [12]. Local recurrence is not an independent prognostic factor in soft tissue sarcoma and this important finding has recently been comprehensively reviewed by Brennan in the Presidential Address of the 49th Annual Cancer Symposium of the Society of Surgical Oncology [13].

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STRATEGIES TO ACHIEVE LIMB SALVAGE

Treatment options for locally advanced extremity soft tissue sarcoma may consist of an amputation or a limb-sparing extensive surgical procedure followed by radiation therapy. This combination may mutilate and compromise limb function considerably. In light of the evidence that amputations do not improve survival, it stands to reason to pursue rigorous methods that will achieve limb salvage. This usually involves some form of induction treatment of the locally advanced tumour in order to render the tumour resectable. A number of options can be considered.

INDUCTION CHEMOTHERAPY AND MULTIMODALITY INDUCTION THERAPY

Eilber and collegues at UCLA combined pre-operative (intra-arterial or systemic) chemotherapy and radiotherapy to improve resectability rates, a strategy later employed and reported on by many other groups. The multidisciplinary programme at UCLA combined pre-operative chemotherapy, radiotherapy followed by resectional surgery and often followed by further adjuvant chemotherapy. The most important conclusions from the UCLA programme are [14]: (1) local control is improved when both pre-operative chemotherapy and radiotherapy are applied; (2) pre-operative radiotherapy of 35 Gy is associated with excellent local control (9% local recurrences), but causes too many complications (fractures); 17.5 Gy is not effective enough (20% local recurrences) and 28 Gy is adequate (14% local recurrences, no fractures); (3) intra-arterial chemotherapy is not more effective than intravenous chemotherapy; (4) high-dose ifosfamide followed by doxorubicin and cisplatin in combination with 28 Gy radiotherapy increases complete recovery (CR) rates from approximately 8% in all previous protocols to more than 40%. It must be stressed that many of the sarcomas reported on could have been resected without induction treatment and that these results were often achieved in patients who had undergone incomplete (debulking) resections of their tumours. This high rate of CRs was therefore achieved on relatively small tumours. The response rates and limb-salvage rates may therefore be misleading in comparison with reports on the treatment of uniformly locally advanced soft tissue sarcoma.

Much lower CR rates are observed in trials on systemic induction chemotherapy involving 'untouched', often large tumours [15, 16]. Various multidrug regimens resulted, in these reports, in an overall response of 60% with complete remission rates of 6–11%. The impact of these treatments on limb salvage is unclear.

Pre-operative radiotherapy may be applied or conventional postoperative radiation therapy may be added in cases with

marginal or positive resection margins. Local recurrences and amputation may also be avoided by applying brachytherapy techniques to the tumour bed in the context of marginal resections [17]. This may well improve local control, but has no impact on survival.

Isolated limb perfusion with TNFα and melphalan induction therapy

Isolated limb perfusions (ILP) with cytostatic agents exposes tumours to drug concentrations more than 20 times higher than after systemic therapy to maximise tumour reduction [18]. ILP may render an irresectable tumour resectable and reduce the local recurrence rate. In cases with widespread metastases, it can be used palliatively for alleviation of pain and to avoid amputation. Melphalan and doxorubicin have been used in the treatment of extremity soft tissue sarcoma, but in general with little success [19].

The application of TNFα in the ILP setting, pioneered by Liénard and Lejeune [20], has changed this situation remarkably. In a multicentre study, results of the initial experience with the triple regimen, i.e. TNF + IFNα + melphalan, were reported in 1993 [21] and 1996 [1]. Two other groups in Europe, one from the U.K. and one from Italy, reported small studies with similar results in 1993 and in 1995 [22, 23]. Very recently the results of 200 perfusions in 186 patients in an eight-center European Cooperative Study in patients with locally advanced soft tissue sarcoma of the extremities treated mainly with TNF + melphalan confirmed earlier reports on the efficacy of this limb-salvaging approach [2]. All tumours were considered to be irresectable or only resectable at the cost of significant loss of limb function. The composition of this series of patients is unusual and demonstrates the irresectability in most patients: large single tumours (median size 16 cm) were present in 143 patients (77%); multifocal primary or multiple recurrent tumours were present in 43 patients (23%), (range 2–100 + tumours); 25 patients (13%) had known systemic metastases at the time of the ILP. Most (161/186) tumours were high-grade tumours and there were 25 grade I sarcomas (always very large, recurrent or multiple). A major tumour response was seen in 82% of the patients rendering most of these large sarcomas resectable. The final outcome as defined by clinical + pathological response was 54 CR (29%), 99 partial recovery (PR) (53%), 29 NC (16%) and 4 PD (2%). At a median follow-up of almost 2 years (22 months) (range 6 + −58 months), limb salvage was achieved in 82%. In 126 patients with a single tumour, the tumour remnant was resected (all marginal resections) and local recurrences developed after 3–24 months in only 14 patients (11%). In the other 60 patients, no resection was performed (multiple tumours, systemic metastases, refusal to be amputated) but local tumour control was obtained in 33 patients (55%) and recurrences occurred in 27 patients (45%). Limb salvage was often still achieved as patients were dying of systemic disease. Additional radiation therapy was given in only 39/186 patients (21%). In 34 patients (18%), the limb had to be amputated.

The basis for these dramatic responses seems in part to be mediated by the total destruction of the tumour vascular bed as can be visualised by angiography [24].

These response rates are far superior to those reported after ILP with chemotherapy alone or after intra-arterial or intravenous induction chemotherapy as discussed above. Moreover in these series, the median tumour size is much lower and patients with multiple tumours are usually not included, whereas almost 25% of the patients in the TNF-ILP series had multiple tumours.

ILP with TNF + melphalan seems of particular palliative value in patients with widespread metastatic disease and an uncontrollably rapidly growing tumour threatening the limb. In all but 2 of 25 such patients, a single ILP provided rapid and life-lasting (up to > 2 years) local control.

CONCLUSIONS

The introduction of TNF in ILP, a single-hit procedure with limited in-patient time and very few general and short-lived side-effects, represents an attractive option in the management of irresectable locally advanced extremity soft tissue sarcoma. Local tumour control is not an independent prognostic factor, but is an important aspect that determines quality of life just like limb preservation. Having both can be achieved in an increasing number of patients. In a patient population that will almost completely be overtaken by the development of systemic metastases, the goal of maintaining as normal a life as possible with the preservation of all limbs is an achievable and very worthwhile goal that should be given due attention and priority in the approach and management of these patients.

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Arbiter

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THE JUDGMENT as to whether a soft tissue sarcoma should be managed with a limb-salvaging resection or an amputation is based on three criteria—the oncological soundness of the procedure, the surgical soundness of the reconstruction and the wishes and lifestyle of the patient.

When the patient presents without evidence of nodal or distant metastases, the oncological soundness of the definitive surgical procedure has been judged by the risk of local recurrence. The presence of a local recurrence has been reported to increase the risk of subsequent metastasis as recently as 1990. In turn, the factors that influence the risk of local recurrence have been identified as the quality of the surgical margin and the response of the patient and the tumour to radiation therapy, chemotherapy or combinations of both. The lowest risk of local recurrence is achieved with a radical margin with an increasing incidence with wide, marginal and intralesional margins when surgery alone is employed. When a satisfactory response to pre-operative radiation therapy is achieved, wide *en bloc* excision for high-grade lesions and marginal *en bloc* excision for low-grade lesions has achieved a modest risk of recurrence (< 10%). The risk of local recurrence after a satisfactory response to chemotherapy appears to be comparable, although the evidence is less convincing than for the more widely used radiation. Intralesional procedures—whether planned debulking, inadvertent contamination or the result of 'shell-out' excisional biopsy—have resulted in unacceptable rates of local recurrence (40–60%). With the premise that local recurrence predisposes to increases in metastasis and decreases in survival, only wide or radical procedures have been deemed adequate, with the caveat that it makes no difference whether the margin is attained by limb salvage or amputation.

The premise that local recurrence correlates unfavourably with survival has recently been challenged by several reports, as pointed out by Eggermont and the need for amputation, when only amputation will obtain a presumably adequate margin, has been denigrated. This difference in opinion is at the heart of the oncological criteria. Unfortunately, as pointed out by Gunterberg (see pp. 2295–2297), the nature of the problem (small numbers of cases, differing histological variants, differing lesion sizes, varying anatomic sites and varying stages) does not allow a firm conclusion based on retrospective evaluations with inadequate statistical methodology. Perhaps only a prospective randomised trial will have the possibility of settling this issue. Such a trial, with the practical and ethical difficulties it presents, is not likely in the near future.

The second issue, that of the functional outcome of amputation versus limb salvage, is perhaps of second importance to life survival. It is quite clear that serious complications that produce functionally unsatisfactory outcomes are much more common following limb salvage, particularly when adjuvant radiation therapy/chemotherapy are employed to facilitate limb salvage. These complications (local recurrence, pathological fracture, unhealed wounds, uncontrolled infection) often lead to repeated surgical procedures occasionally ending in an amputation.

In some anatomic sites, especially in the lower extremity below the knee, artificial limbs are functionally superior to limb-salvaging procedures that require significant neurological or skeletal loss. It is also quite clear that the functional outcome of a primary planned amputation is significantly better than that of a secondary, unplanned amputation.

The third issue, the customising of the procedure to the needs and desires of the individual patient, has not received