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REVIEW ARTICLE

Chemotherapy for Non-metastatic High-grade Osteosarcoma of Extremity — Is Neoadjuvant Better than Adjuvant?

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ABSTRACT

The addition of adjuvant or neoadjuvant chemotherapy to surgery revolutionises the treatment of high-grade non-metastatic osteosarcoma of the extremities. Overall 5-year survival of more than 50% to 60% is now a realistic achievable goal. Neoadjuvant chemotherapy possesses the theoretical advantages of optimising surgical results, providing early treatment of micrometastases, allowing histological assessment of chemotherapy, and customising postoperative chemotherapy. In this paper, the literature is reviewed to explore the existence of any comparative benefit of neoadjuvant over adjuvant chemotherapy for this disease entity.

Key Words: *Chemotherapy, adjuvant, Neoadjuvant therapy, Osteosarcoma, Extremeties*

INTRODUCTION

Despite the rarity of high-grade non-metastatic osteosarcoma of the extremities, the past 3 decades have witnessed a significant evolution of treatment for this condition. Close scrutiny of the medical literature in the early 1970s reveals only a few reports with a 5-year survival rate exceeding 20% after surgery alone,[1-4] except for 1 from the Mayo Clinic.[5] In a review of more than 1000 patients treated by surgery alone, more than 80% of recurrences occurred in the lung within the first 2 years after treatment, suggesting the presence of micrometastases at the time of or before surgery.[6] Indeed, the myth of whether there had been a change in the natural history of the disease once speculated by Taylor et al could be explained by the improvement in preoperative staging of the thorax.[5]

ADJUVANT CHEMOTHERAPY

So unsatisfactory were the surgical results that Edmonson et al from the Mayo Clinic conducted the first randomised study of adjuvant chemotherapy, which was published in 1980.[7] However, this author was not able to improve either the 2-year disease-free or overall survival by adding high-dose methotrexate (HDMTX) after amputation. The major breakthrough came in 1986 when Link et al reported on the efficacy of postoperative multi-drug combination chemotherapy.[8] The combination of HDMTX, cisplatin, adriamycin, and bleomycin/cyclophosphamide/actinomycin D (BCD) was reported to confer a statistically significant 2-year actuarial relapse-free survival benefit over the control group (66% vs 17%) in a small randomised study consisting of 36 patients. Seventy seven other patients, who were not randomised but chose their treatment options, were also followed and a similar trend of difference in results was observed. Although there was no benefit in initial overall survival, an updated report in 1991 showed a significant overall survival advantage at 6 years in favour of adjuvant chemotherapy (71% vs 50% for the control group; $p = 0.05$).[9] The advantage for the chemotherapy group in 6-year event-free survival was also maintained with statistical significance. At almost the same time as Link et al's first report,[8] Eilber et al reported a similar benefit in 2-year disease-free and overall survival in another randomised study of similar size and design.[10] Since then, the role of postoperative adjuvant multi-drug chemotherapy has become established and this has led to the indoctrination of adjuvant chemotherapy in the treatment protocols for localised osteosarcoma of the extremity in almost all institutions.

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Table 1. Treatment results of studies using neoadjuvant chemotherapy for non-metastatic extremity osteosarcoma.

Study	Disease-related survival	Overall survival
Winkler et al[14] (COSS-80)	68% (30-month DFS)	
Provisor et al[15] (CCG-782)	56% (8-year EFS)	60% (8-year)
Winkler et al[16] (COSS-82)	58% (4-year MFS)	
Bramwell et al[17] (1st EOI)	57%* (5-year DFS)	64%* (5-year)
Souhami et al[18] (2nd EOI)	44% (5-year PFS)	55% (5-year)
Saeter et al[19] (SSGS)	54% (5-year RFS)	64% (5-year)
Meyers et al[20] (MSK T10)	76%† (5-year DFS)	
Meyers et al[21] (MSK T12)	78% (5-year EFS)	
Ferrari et al[22] (IOR-OS1)	46% (12-year DFS)	53% (12-year)
Bacci et al[23] (IOR-OS2)	59% (10-year EFS)	70% (10-year)
Ferrari et al[24] (IOR-OS3)	54% (8-year EFS)	61% (8-year)
Bacci et al[25] (IOR-OS4)	75% (3-year DFS)	91% (3-year)
Fuchs et al[26] (COSS-86)	66% (10-year EFS)	72% (10-year)

Abbreviations: DFS = disease-free survival; EFS = event-free survival; MFS = metastasis-free survival; PFS = progression-free survival; RFS = relapse-free survival; COSS = Cooperative German-Austrian-Swiss Osteosarcoma Study Group; CCG = Children's Cancer Group; EOI = European Osteosarcoma Intergroup; SSGS = Scandinavian Sarcoma Group Study; MSK = Memorial Sloan-Kettering; IOR-OS = Istituto Ortopedico Rizzoli - Osteosarcoma protocol.
* Figures for the group receiving 6 cycles of doxorubicin and cisplatin.
† Figure for patients aged 21 years or younger.

Concept of Neoadjuvant Chemotherapy

The concept of postoperative adjuvant chemotherapy being effective at eradicating micrometastases slowly evolved in 1976 when Rosen et al first reported the efficacy of preoperative vincristine, adriamycin, and weekly HDMTX.[11] In this T5 protocol, 17 of 18 patients were reported to have tumour shrinkage after preoperative chemotherapy, which was originally designed to provide treatment for patients waiting for the custom-made prosthesis necessary for limb-sparing surgery. Jaffe et al also observed a 60% clinical and/or radiological response by the primary tumour when treated with weekly HDMTX.[12]

In the T7 protocol, a more aggressive schedule of preoperative BCD, weekly-HDMTX, vincristine, and adriamycin was given as neoadjuvant chemotherapy.[13] After surgery, the same chemotherapy was repeated for 3 more cycles. In an attempt to further improve the outcome for poor responders to preoperative chemotherapy, Rosen et al modified the postoperative adjuvant chemotherapy in the T10 protocol according to the histological response reported as percentage of tumour necrosis in the resected primary tumour.[13] An adriamycin/cisplatin combination became the key components of the postoperative multi-drug armamentarium for the poor responders. The attractive possibility of 'individualising' chemotherapy and prognosticating patients according to the primary tumour necrosis rate established the popularity of this neoadjuvant chemotherapy approach in the 1980s and 1990s.

Indeed, an overview of the literature as summarised in Table 1 indicates that an event-free survival of approximately 40% to 60% can be achieved with this approach,[14-26] although the best results from Memorial Sloan-Kettering (MSK) have never been reproduced.[20,21] Before accepting the orthodox status of this neoadjuvant approach, it would be prudent to critically analyse the underlying rationale as well as to cross-examine the evidence available in the medical literature documenting the extent of how the theoretical advantages have been validated.

Theoretical Advantages of Neoadjuvant Chemotherapy

Optimising Surgery

The theoretical advantages of neoadjuvant chemotherapy over conventional adjuvant chemotherapy are listed in Table 2. Firstly, surgery can be optimised by delivering up-front neoadjuvant chemotherapy. This allows ample time (approximately 6 to 8 weeks) for fabricating custom-made prosthesis if amputation is still contemplated for neurovascular bundle invasion

Table 2. Theoretical advantages of neoadjuvant chemotherapy.

• Buys time for optimisation of surgical results
• Treats micrometastases early without having to wait for wound healing
• Histological tumour response is the most significant prognostic predictor of relapse-free survival
• Provides opportunity to customise postoperative chemotherapy according to primary chemotherapy response

Table 3. Proportion of patients receiving limb-sparing surgery in various studies.

Study	Percent of patients undergoing limb-sparing surgery	Year published
Winkler et al[16] (COSS-82)	43%	1988
Winkler et al[27] (COSS-86)	42%	1990
Saeter et al[19] (SSGS)	23%*	1991
Bramwell et al[17] (1st EOI)	66%	1992
Bacci et al[23] (IOR-OS2)	83%†	1993
Souhami et al[18] (2nd EOI)	72%	1997
Provisor et al[15] (CCG-782)	43%	1997
Bacci et al[25] (IOR-OS4)	97%†	1998

Abbreviations: COSS = Cooperative German-Austrian-Swiss Osteosarcoma Study Group; SSGS = Scandinavian Sarcoma Group Study; EOI = European Osteosarcoma Intergroup; CCG = Children's Cancer Group; IOR-OS = Istituto Ortopedico Rizzoli - Osteosarcoma protocol.
* High-dose methotrexate as the only preoperative chemotherapy.
† Preoperative intra-arterial cisplatin given in IOR-OS2 and optional in IOR-OS4.

or pathological fracture with extensive soft tissue infiltration. When limb sparing surgery is planned, which is possible for at least 40% to 80% of patients, as shown in Table 3,[15-19,23,25,27] preoperative chemotherapy also allows time for detailed planning of reconstructive surgery using customised endoprosthesis.

In addition, the primary tumour could also be reduced to the extent that limb-sparing surgery is possible after preoperative chemotherapy for up to 40% of patients originally planned for amputation, as reported in the 2nd European Osteosarcoma Intergroup (EOI) study.[18]

Furthermore, it has been shown that the nature of primary tumour response to neoadjuvant chemotherapy correlated closely with local control. Bacci et al, in reviewing 540 patients, showed that in addition to adequacy of resection margins, the 7-year locoregional relapse-free survival was also significantly related to the degree of chemotherapy response to preoperative chemotherapy.[28] This researcher concluded that immediate amputation was necessary if the surgical margin was inadequate, especially for those patients for whom the response to chemotherapy was also poor.

Early Treatment of Micrometastases

Early treatment of occult micrometastases without having to wait 3 to 4 weeks for the consequences of initial primary surgery is, without doubt, another important advantage of neoadjuvant chemotherapy. More importantly, there is evidence to show that the histological tumour response to neoadjuvant chemotherapy allows prognostication of patient outcome. Although there have been minor variations in the definition of good responder (Table 4),[13,16-19,22-25,27] more than 90% tumour necrosis has been shown to be a significant prognostic factor for favourable outcome. In a critical review of 8 chemotherapy studies published between 1973 and 1992,[29] chemotherapy response of more than 90% tumour necrosis emerged as the most important prognostic factor for disease-free survival. Indeed, there is an advantage of at least an additional 30% in 5-year event-free and overall survival for the good over the poor responders to neoadjuvant chemotherapy (Table 5).[15-17,19-23,25,27]

However, the underlying hypothesis to support the legitimacy of using primary tumour response as a surrogate marker to predict final patient outcome in terms

Table 4. Definition of good response in various studies.

Study	'Good' response definition
Rosen et al[13] (MSK)*	Grade III = scattered foci of tumour cells among necrosis, Grade IV = complete necrosis
Saeter et al[19] (SSGS)	Grade III = scattered foci of tumour cells among necrosis (roughly >90% necrosis), Grade IV = complete necrosis
Winkler et al[16,27] (COSS-82/86)	Favourable = ≥90% tumour necrosis
Bramwell et al,[17] Souhami[18] (EOI)	No tumour or D1
Bacci et al[23,25] (IOR)† Ferrari et al[22,24] (IOR)	Good = 90% - 99% necrosis Total = 100% necrosis
Provisor et al[15] (CCG)	Grade III = >95% necrosis, Grade IV = 100% necrosis

Abbreviations: MSK = Memorial Sloan-Kettering; SSGS = Scandinavian Sarcoma Group Study; COSS = Cooperative German-Austrian-Swiss Osteosarcoma Study Group; EOI = European Osteosarcoma Intergroup; IOR-OS = Istituto Ortopedico Rizzoli - Osteosarcoma protocol; CCG = Children's Cancer Group; D1 = relatively acellular hyalinised tissue containing widely scattered pleomorphic/pyknotic cells.
* MSK T12 and †IOR-OS4 protocols stressed that difference between grade III and IV was more significant than that between II and III, so that salvage alternative chemotherapy should be given for all other than grade IV (total necrosis).

Table 5. Outcome of patients classified by primary chemotherapy response in various studies.

Study	Good responders		Poor responders		Rate of good responders
	5-year EFS	5-year OS	5-year EFS	5-year OS	
Provisor et al[15] (CCG-782)	81%	87%	48%	55%	28%
Bramwell et al[17] (1st EOI)	80%	85%	38%	46%	30%
Saeter et al[19] (SSG)	71%	89%	53%	58%	17%*
Winkler et al[16] (COSS-82)	77%†		44%†		(60/26%)†
Winkler et al[27] (COSS-86)	75%	80%	51%	56%	68%
Meyers et al[20,21] (MSK T4, T5, T7, T10, T12)	80%‡	63%‡			42% (19/51%)‡
Ferrari et al[22] (IOR-OS1)	61%§		30%§		52%
Bacci et al[23] (IOR-OS2)	62%		51%		71%
Bacci et al[25] (IOR-OS4)	74%‖	88%‖	55%‖	58%‖	(32/51%)‖

Abbreviations: EFS = event-free survival; OS = overall survival; CCG = Children's Cancer Group; EOI = European Osteosarcoma Intergroup; SSGS = Scandinavian Sarcoma Group Study; COSS = Cooperative German-Austrian-Swiss Osteosarcoma Study Group; MSK = Memorial Sloan-Kettering; IOR-OS = Istituto Ortopedico Rizzoli - Osteosarcoma protocol.

* Only high-dose methotrexate used in preoperative chemotherapy.

† Four-year metastasis-free survival rates — 60% and 26% for those given doxorubicin/cisplatin group and bleomycin/cyclophosphamide/actinomycin D, respectively, were good responders.

‡ Crude survival for all T4, T5, T7, T10, T12 protocols included, 19% good responders for high-dose methotrexate only as preoperative chemotherapy and 51% for multi-drug preoperative chemotherapy.

§ 12-year disease-free survivals reported.

‖ Crude 4-year disease-free survival and overall survival for grade IV as good responders vs grades I, II, and III combined as poor responders — 32% and 51% had grade IV and grade III response, respectively.

of relapse-free survival has never been formally addressed. Only recently was the concordance of chemosensitivity between primary and lung metastases explicitly assessed.[30] Bacci et al reported that only 4% of good responders for primary tumour had a poor response for lung metastases.[30] Conversely, 58% of good responders for lung metastases had a poor response for primary tumour. Therefore, there is no absolute, but nevertheless a high, correlation for chemosensitivity between primary and metastatic osteosarcoma within the same patient. This correlation indicates that the occult micrometastases for good responders are more liable to be eradicated and therefore supports the use of primary chemotherapy response as a significant prognostic factor to predict final outcome.

Histological Response Assessment

Given the importance of primary tumour response, it is a logical strategy to pursue improved patient outcome through increasing the proportion of good responders. This can be achieved by early introduction of more active drugs. This approach is preferred to purely intensifying the dose of 1 or 2 drugs, as the received preoperative dose or dose-intensity of the 2-drug regimen used in the 2 EOI studies were found not to influence histological response when the results were retrospectively analysed.[31] On the other hand, in the Istituto Ortopedico Rizzoli (IOR) OS4 protocol from Bologna[25] and Cooperative German-Austrian-Swiss Osteosarcoma Study Group (COSS)-86 study,[26,27] when all 4 active drugs of ifosfamide, cisplatin, adriamycin, and high dose methotrexate were employed up-front, a 'good' histological response of 83% and 69%, respectively, was produced.

A second approach to maximising tumour response is to prolong the duration of preoperative chemotherapy as practised in Rosen et al's T7 protocol.[11] The T7 protocol undoubtedly induced more tumour necrosis than protocols with shorter induction chemotherapy such as T10.[20] However, the disease-free survivals of these 2 protocols were not found to be different. Indeed, the correlation of outcome with histological response to preoperative chemotherapy was lost upon longer duration of preoperative chemotherapy, so much so that the difference in disease-free survival between good and poor responders converged as the duration of preoperative chemotherapy increased.[20]

The third approach would be to directly increase the dose intensities of both preoperative and postoperative chemotherapy with growth factor support. This approach is currently assessed by 2 ongoing clinical trials. The EOI trial is randomising patients to receive combination doxorubicin and cisplatin every 2 weeks with granulocyte-colony stimulating factor (G-CSF) support, or the same combination every 3 weeks without G-CSF, while the 3-group study of the Paediatric Oncology Group (POG) is currently comparing different dose-intensities (and different numbers) of drugs, used both preoperatively and postoperatively.

Lastly, intra-arterial (IA) administration of cisplatin has been reported to be able to increase the drug concentration to the tumour by 1.5 to 4 times that achieved by the intravenous (IV) route. The benefit derived from this higher tissue drug concentration is still controversial, as the dose-response relationship of osteosarcoma for cisplatin at the dose level of 90 to 150 mg/m^2 through either the IA or IV route has not been exclusively demonstrated. In the COSS-86 study, neither increased tissue deposition of cisplatin nor raised serum cisplatin level was documented for the IA route of administration.[27] Although strict randomisation was not possible, there was no statistically significant difference for the proportion of good responders (68% vs 69%), 10-year event-free survival (63% vs 70%), or overall survival (67% vs 75%) between the IA and IV groups, respectively.[26] Similarly, despite achieving a higher rate of grade III or more responses (without an associated improvement in the rates of limb salvage, local recurrence, and event-free survival, however) using IA instead of IV cisplatin in the 3-drug neoadjuvant chemotherapy regimen, there was no such difference for the more aggressive 4-drug regimen at IOR.[32] Pharmacokinetic studies documenting a simultaneous increased drug concentration and uptake in the primary tumour and the sites harbouring occult metastases are definitely instrumental to clarify the uncertainties behind this approach.

Customising Postoperative Chemotherapy

Providing an opportunity to customise postoperative chemotherapy according to primary tumour response is the last (but often regarded as the most important) advantage of neoadjuvant chemotherapy. The benefit, if realised, can be 2-fold. Alternative non-cross resistant chemotherapy can be switched to postoperative treatment for poor responders, while less intensive and toxic chemotherapy can be given to good responders. To this end, the last 3 cycles of postoperative chemotherapy are omitted for good responders in the most recent IOR-OS4 protocol in Bologna to reduce toxicities.[25] In attempts to 'salvage' the poor responders, cisplatin frequently replaced HDMTX (with or without BCD) in Rosen et al's T10 protocol or variants used in studies by MSK,[13,20] the Scandinavian Sarcoma Group,[19] the EOI,[17,18] and COSS-82.[16] Ifosfamide-based chemotherapy was used either as a substitute or as additional chemotherapy in other studies (COSS-82)[16] or protocols (IOR-OS2).[23]

Such a 'salvage' approach, however, results in conflicting and predominantly disappointing results as reported from MSK,[20] Scandinavian Sarcoma Group,[19] Children's Cancer Group (CCG),[15] and COSS-82.[16] The experience from COSS-82 is particularly illustrative.[15] In that study, withholding cisplatin/doxorubicin preoperatively for the experimental group produced a lower rate of good responses. Despite introduction of cisplatin/doxorubicin for the poor responders, the actuarial 5-year metastasis-free survival rate of patients in the experimental group as a whole was inferior to that of the control group (45% vs 68%; $p < 0.05$), and also inferior to the prior COSS-80 study in which no salvage chemotherapy was delivered for the poor responders.[14] The salvage strategy employed was regarded by the authors to be a failure. Only IOR-OS2 reported a possible benefit in modifying the postoperative chemotherapy regimen.[23] Upon adding an ifosfamide/etoposide combination, these researchers suggested an improved disease-free survival for the poor responders when analysis was limited to those adequately treated. The discrepancy in event-free survival, although statistically insignificant ($p = 0.08$), showed a trend favouring the good responders.

Disadvantages of Neoadjuvant Chemotherapy

There are potential disadvantages in using up-front neoadjuvant chemotherapy and delaying definitive surgery for the primary tumour. The delay of 6 to 10 weeks can potentially allow haematogenous spread of drug-resistant clones. No chemotherapy regimen, however effective, can measure up to the completeness and readiness of surgical extirpation for control of the primary tumour.

Moreover, surgical complications after neoadjuvant chemotherapy are not infrequent, especially for those undergoing limb-sparing surgery. Bacci et al found that 63% of patients receiving preoperative neoadjuvant chemotherapy containing intra-arterial cisplatin had at least 1 postoperative complication, most of which required additional surgery.[23] In the second EOI study, in which preoperative chemotherapy was employed, 23% of patients conservatively operated (vs 12% undergoing amputation) were found to have surgical complications.[18] The affected patients might suffer a longer delay in resumption of postoperative chemotherapy than is stipulated in the protocol, possibly adversely affecting overall results.

Lastly, the unavoidable gap between the termination of neoadjuvant chemotherapy and resumption of postoperative adjuvant chemotherapy as specified in protocols is often in the order of at least 3 or more weeks.

The increased surgical complications after neoadjuvant chemotherapy mentioned earlier can further lengthen the drug-free period, thereby reducing the overall drug dose intensities, allowing tumour repopulation in micrometastases and promoting emergence of drug-resistant clones. Meyers et al reported a possible adverse impact on disease-free survival when there was a delay of more than 24 days in resuming postoperative chemotherapy for those with grade I/II responses.[20]

Review of Evidence in the Medical Literature

The only randomised study comparing neoadjuvant and adjuvant chemotherapy approaches failed to detect any difference in outcome.[33] The preliminary results of the POG 8651 study has been reported in an abstract form. From 1986 to 1993, 106 patients were randomised to receive neoadjuvant chemotherapy (10 weeks of 2 cycles of high dose methotrexate, cisplatin, and adriamycin) followed by surgery and postoperative chemotherapy, or immediate surgery plus postoperative chemotherapy with duration equivalent to that of the neoadjuvant group. There was no difference in either the 2-year or 5-year event-free survival. The 5-year event-free survival for the neoadjuvant group was 61.6% whereas that for the adjuvant group was 69.3%.

In reviewing the non-randomised data, which nevertheless constituted the vast majority of the current body of evidence, it is also difficult to establish any unyielding benefit of neoadjuvant chemotherapy. Disease-free survival of sequential studies from MSK was compared. There was no significant difference between those obtained from the T4 protocol (adjuvant) and the T5, T7, T10, or T12 protocols (neoadjuvant plus adjvant).[20] The adjuvant chemotherapy approach used in the CCG-74 study[34] reported in 1987 again failed to demonstrate results inferior to the neoadjuvant protocol of the CCG-782[15] published in 1997. Similarly, the continuously disease-free actuarial curve of the 127 patients treated by preoperative multi-drug chemotherapy including IA cisplatin at IOR was not different from that of an earlier group of 106 patients treated by postoperative adjuvant chemotherapy at the same institute.[35]

In the COSS-82 study reported by Winkler et al, 22 patients given postoperative chemotherapy only for various reasons had disease-free survival similar to the 66 patients randomised to receive the more aggressive neoadjuvant chemotherapy in the control group.[16] There was also no difference in disease-free survival between the 63 patients not receiving neoadjuvant chemotherapy when compared with those who received the neoadjuvant protocol in MSK.[20] Lastly, the survival for the 127 patients treated with neoadjuvant chemotherapy at IOR was not much different from the survival observed for 27 contemporary patients who refused preoperative chemotherapy and were treated with immediate surgery followed by chemotherapy.[35]

Current Status and Future Development of Chemotherapy for Osteosarcoma

Chemotherapy, given either as adjuvant or neoadjuvant therapy, definitely revolutionised the treatment of high grade non-metastatic osteosarcoma of the extremities. At least 30% to 40% of such patients can have their micrometastases eradicated by chemotherapy at presentation. While neoadjuvant chemotherapy confers additional theoretical benefits over adjuvant chemotherapy, these have not been convincingly demonstrated by the available evidence in the medical literature.

The use of neoadjuvant chemotherapy, surgery, and then adjuvant chemotherapy, however, certainly achieves long-term cure for more than half of the patients who presented with previously untreated non-metastatic osteosarcoma of the extremity and trunk.[36] It has been shown that both good response to preoperative neoadjuvant chemotherapy and negative surgical margins (both factors likely to be favourably influenced by aggressive preoperative neoadjuvant chemotherapy) can predict good local control after limb-sparing surgery.[28] Furthermore, neoadjuvant chemotherapy helps experienced surgeons to conserve the affected limb by reducing the rate of amputation without jeopardising local control. Moreover, omitting neoadjuvant chemotherapy will lose the opportunity to assess the histological response to neoadjuvant chemotherapy, which emerged as one of the most important prognostic factors for long-term outcome.[36]

All in all, it is likely that the approach of neoadjuvant chemotherapy followed by definitive limb-sparing surgery (if possible) and then adjuvant chemotherapy will prevail. Identification of potential molecular markers at the time of diagnosis, including HER2/erbB-2 expression,[37] P-glycoprotein assay,[38] and loss of heterozygosity of the Rb gene,[39] to predict poor outcome before rather than after chemotherapy is an important step towards selecting high-risk patients for more aggressive dose-intensive multi-drug neoadjuvant chemotherapy or other experimental treatment. Alternatively, non-invasive imaging procedures that can

assess the initial chemotherapy response early in the course of treatment should be explored to allow early introduction of 'salvage' chemotherapy or immediate surgery rather than to wait for histological assessment when only postoperative adjuvant chemotherapy can be modified. The role of modalities such as dynamic magnetic resonance imaging,[40] positron emission tomography,[41] or Thallium isotope[42] in assessing chemotherapy response is being validated by histological correlation.

CONCLUSION

During the past decade, the result of 60% to 70% 10-year survival for non-metastatic high grade osteosarcoma of the extremities now achievable with state-of-the-art chemotherapy and surgery is gratifying. However, oncologists should not remain complacent and must be prepared to meet the future challenge of managing severe late complications such as cardiomyopathy, second malignancy, and infertility at follow-up,[22] as well as searching for more effective treatment for those aggressive tumours that fail to respond to the current strategies.

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