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Paediatric Update

Osteosarcoma

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INTRODUCTION

OSTEOSARCOMA IS the most common primary bone malignancy affecting children and young adults. Their outlook, compared with the results of treatment available 25 years ago, has been dramatically improved by modern combined modality therapy. However, up to half the patients with osteosarcoma are still not cured and many questions surrounding optimal management remain. Recently, there has been a rapid expansion in our knowledge of the biology of osteosarcoma which it is hoped will soon translate into improved treatment.

AETIOLOGY AND PATHOGENESIS

Epidemiology and aetiology

Although often regarded as primarily a disease of childhood, osteosarcomas continue to occur throughout adulthood (Figure 1). Recent figures from the United States suggest the incidence to be 0.3/100 000 [1]. This is in accordance with cancer registry figures from the U.K. Although the peak incidence occurs at a slightly earlier age in girls (10–14 years) than boys (14–18), there remains a near 2-fold male preponderance. Axial tumours are more common in adults; sarcomas complicating Paget's disease are thought to be responsible for at least some of these tumours in the elderly but published information is sparse [2, 3].

No predisposing factor is identifiable in most patients. The risk of an osteosarcoma occurring in survivors of heritable retinoblastoma has been accurately defined [4–7]. Exposure of these patients to therapeutic radiation and alkylating agents in infancy is a powerful co-factor with most but not all osteosarcomas occurring within a previously irradiated field [8]. Radiation-induced sarcomas occur in other settings, particularly after treatment of breast and gynaecological cancers [9]. Osteosarcoma is the most common histological pattern in this setting but even so the incidence is only of the order of 1:5000. Finally, sarcomas are among the spectrum of tumours seen in families with germline mutations of the tumour suppressor gene, *p53* [10, 11]. Such families are rare and, together with sporadic cases of germline *p53* mutation, may account for only 3% of osteosarcomas [12, 13].

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Biology

The relationship to rapid bone growth illustrated by the predilection of osteosarcoma for the proximal humerus and sites around the knee remains unexplained. The pathological and clinical heterogeneity of osteosarcoma has long been recognised by those regularly involved in the management of these tumours. This is now mirrored by the findings of cellular and molecular biologists. Osteosarcomas have no characteristic cytogenetic abnormality. Instead, comparative genomic hybridisation studies have revealed very complex chromosomal changes [14]. Normal bone differentiation and development involves members of the *AP-1* gene family [15]. Transgenic mice overexpressing the proto-oncogene *c-fos* develop osteosarcoma almost without exception and overexpression of this oncogene has been detected in human osteosarcomas [16, 17]. Alterations in expression or function of a variety of other genes have also been described. The best characterised genetic alteration affects the retinoblastoma gene with loss of heterozygosity detectable in more than 50% of tumours [18–22]. Various genes involved in cell cycle regulation may also be affected, particularly *p53*; in other tumours, a greater influence of genes such as *CDK4* and *SAS* is apparent (Figure 2) [23–25].

Studies on the control of osteoblast function are unravelling the complex interaction between growth factors such as insulin growth factor 1, transforming growth factor β1 and epidermal growth factor. IGF-1 is the major mediator of growth hormone action on skeletal growth and this molecule may be involved in the proliferation of osteosarcomas [26]. Inhibition of IGF-1 by growth hormone antagonists has been reported to inhibit proliferation of human osteosarcoma cell lines [27, 28] and phase I studies of a somatostatin analogue have begun in patients with advanced osteosarcoma [29].

CLINICAL ASPECTS AND STAGING

Prognostic factors

The extent of disease at diagnosis is the most powerful determinant of outcome. Few patients in whom metastases are detected by initial staging investigations are cured. Patients presenting with pelvic or other axial tumours also fare badly, primarily because achieving local control is so difficult. Finally, local recurrence is virtually always associated with the co-existence or subsequent development of distant disease.

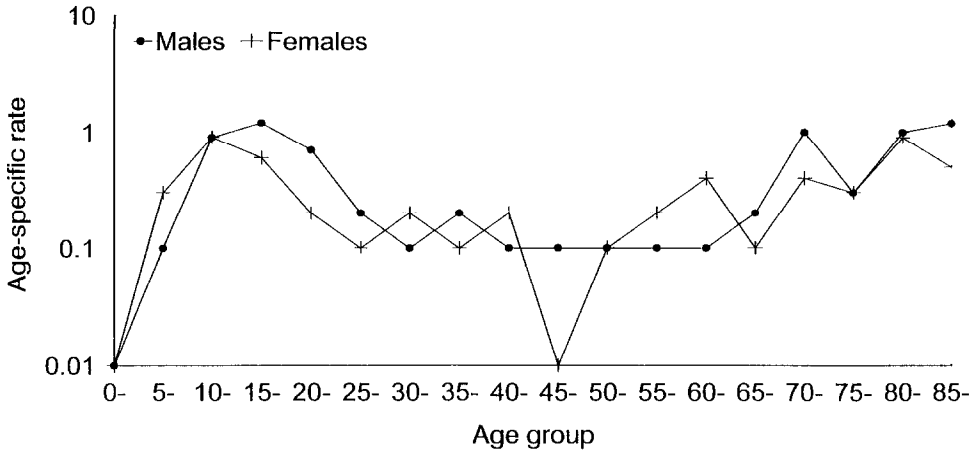

Figure 1. Age-related incidence of osteosarcoma. A log scale has been used for incidence. The peak occurs in teenagers and young adults but cases continue to occur throughout adulthood. Previous irradiation and Paget's disease are risk factors in the elderly. (Source: Thames Cancer Registry).

It has long been recognised that the degree of chemotherapy-induced necrosis detected by careful histological analysis is a very powerful indicator of subsequent outcome for patients with localised extremity lesions who receive chemotherapy before resection of their primary tumour [30]. Despite variations in the definition of response and the inevitable subjective component of such analyses [31–33], this has been consistently reported by all major single centres and in large multicentre randomised trials. The typical discrimination provided by this factor for a single centre, a cooperative group and in a multicentre randomised trial is shown in Table 1. Defining chemotherapy that maximises tumour necrosis and treatments to rescue those with a poor histological response remain primary goals of current clinical research in osteosarcoma. Histological response can only be determined after a significant period of chemotherapy has been completed and this necessitates the continued search for other reliable early predictive factors.

Many other factors have been reported to be associated with differences in outcome [34]. High-grade osteosarcomas have a significantly worse outlook than the rarer low-grade variants. However, additional information is only occasionally provided by defining histological variants within high-grade tumours. Lesions of the proximal femur and humerus are associated with a poorer outcome than those of the distal femur and tibia. Age is probably of less significance than previously believed, with results being skewed by the exclusion of older patients from many clinical studies. Raised plasma LDH (lactate dehydrogenase) and alkaline phosphatase levels both add some adverse prognostic information [35–39].

In contrast to Ewing's sarcoma, tumour size is infrequently used as a prognostic factor, not least because of the difficulties associated with obtaining accurate and complete data in large groups of patients and a lack of consensus as to what measure of tumour size is most appropriate. A recent retrospective analysis from the German cooperative group suggests that absolute tumour volume, measured using plain radiographs, could be used to separate groups of patients with widely differing metastasis-free survival, and when combined with histological response, appears to provide a possible basis for selecting differing therapeutic strategies [40]. The methodology is associated with numerous biases but demands further study.

Methotrexate has been a component of most chemotherapy regimens for osteosarcoma since descriptions of its exceptional activity in this disease were published in the early 1970s [41]. Debate continues about its current role [42–44].

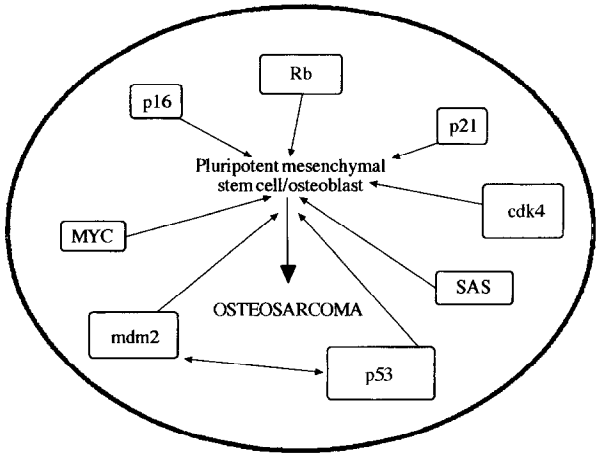

Figure 2. A number of genetic abnormalities have been detected in human osteosarcoma, many affecting genes involved in the control of the cell cycle. The interplay between some of these, e.g. *p53* and *mdm2*, may help predict clinical behaviour for individual tumours.

Table 1. Five-year disease-free survival by histological response to pre-operative chemotherapy. Figures are shown for a specialist single centre, the Memorial Sloan Kettering Hospital (MSK); for an open study of a cooperative study group, the Children's Cancer Study Group (CCSG); and for a multicentre randomised study carried out by the European Osteosarcoma Intergroup (EOI)

Study centre [Ref.]	Extent of necrosis	
	<90%	>90%
MSK [126]	67	93
CCSG [80]	48	81
EOI [73]	45	75

An association between peak serum methotrexate levels and prognosis has been repeatedly reported, mostly on the basis of single-centre studies and retrospective analyses [45–47]. The failure of other groups to confirm this unique importance for methotrexate has been variously ascribed to inadequate dose, overhydration and failure to adjust individual doses on the basis of peak serum levels. Although methotrexate is a highly active drug in this disease, current data are of insufficient quality to support the notion that its effective administration is the most important factor to influence outcome.

In the future, greater reliance may be made on the prognostic information provided by a growing list of biological markers. As already mentioned, alterations in the *Rb* gene are common in human osteosarcoma. Feugeas and associates have reported a pilot study to determine the predictive value of loss of heterozygosity (LoH) at the *Rb* gene [48]. LoH was found in 24 of 34 cases with an associated event-free survival of 63% compared with 100% for those patients in whose tumour no LoH could be demonstrated. No correlation was apparent between changes in *Rb* and histological response. This is now the subject of a prospective study in France. Onda and associates detected expression of ErbB-2 protein in 11 of 26 patients with osteosarcoma which appeared to correlate with the early development of pulmonary metastases and inferior survival [49]. The importance of the c-*erb*B-2 proto-oncogene in other solid tumours, particularly breast cancer, warrants the validation of this observation in a larger group of patients.

A further area of interest has emerged from studies of multidrug resistance. Investigators in Bologna have used immunohistochemistry to measure P-glycoprotein expression in osteosarcoma. Increased expression of P-glycoprotein was associated with a significantly inferior event-free survival and in a multivariate analysis, P-glycoprotein status and the extent of histological response were independent prognostic factors [50]. Although further supportive studies have appeared from the same group, excitement about the possible therapeutic potential for such an observation must be tempered by the poor results of multidrug resistance modification in other tumour types [51, 52]. The possibility of P-glycoprotein status being a surrogate marker for biological behaviour may not diminish its value as a component in a battery of prognostic factors.

The adaptation of therapy for localised extremity osteosarcoma on an individual basis using information from various prognostic factors remains a distant goal. There are certainly enough candidate factors and it is possible that international collaboration, as has been used in other tumours, might result in data with sufficient statistical power to produce an acceptable and valid index. Unfortunately, the therapeutic adjustments that might be made on the basis of such an index are currently limited.

Staging

The Enneking system remains in widespread use, but its discriminatory power is limited as most patients fall into the IIb category [53]. Initial imaging of the primary tumour is with plain radiography and magnetic resonance imaging. Radionucleotide bone scanning and computed tomography (CT) of the thorax are necessary to exclude metastatic disease. Spiral CT may be significantly more sensitive than conventional CT, resulting in some stage migration of patients [54]. Other parameters of disease activity such as alkaline phosphatase and lactate dehydrogenase may in future be incorporated alongside biological markers to provide a more clinically valuable staging system.

Imaging

There is great potential for modern imaging methods to aid accurate evaluation of response to pre-operative chemotherapy. Advances in magnetic resonance imaging techniques which may provide more helpful information have yet to be fully validated [55–57]. Others have reported the use of 201-thallium [58–61] or fluorodeoxyglucose-position emission tomography (FDG–PET) [62] scanning to provide early prediction of histological response and certainly the results are promising, but once again well-designed studies to define the role of such techniques, most of which are demanding for patients and expensive, are awaited. Colour flow Doppler scanning may be a more acceptable alternative [63, 64].

TREATMENT

Surgery of primary tumour

Nowadays, most children and young adults with extremity osteosarcoma can expect to be considered for a limb salvage procedure rather than amputation. It is well recognised that chemotherapy given prior to surgery can increase the chances of a successful limb salvage operation. The impact of the timing of surgery has been addressed by a Pediatric Oncology Group randomised trial which showed no survival disadvantage when all chemotherapy was given after surgery [65]. Notably, in this valuable but difficult-to-conduct study, the amputation rate in both arms was nearly 50%. The effect of a more protracted delay in the delivery of chemotherapy, to the time of recurrence, can be inferred from the Multi-institutional Osteosarcoma study, in which the large advantage for relapse-free survival of early chemotherapy only translated into an overall survival advantage after prolonged follow-up [35, 66].

The functional quality of life and economic advantages of limb salvage versus amputation remain a subject of study and debate. The rate of re-operation appears to be very high by 10 years for recipients of endoprostheses. Technical advances in biological reconstruction are very promising but the availability of such approaches is limited to a few centres.

Rates of local recurrence for limb salvage surgery are now extremely low, certainly less than 10% in specialist centres. However, the dismal outcome for those in whom a local recurrence occurs is widely recognised, with very few such patients achieving long-term survival [67, 68]. Local recurrence appears to be a marker of biological behaviour and heralds distant metastases. In light of this, a key surgical question is whether patients at risk of local recurrence can be identified earlier and then whether more radical surgical intervention can alter prognosis.

Chemotherapy

Up to 20% of patients with osteosarcoma are cured without chemotherapy [35, 69]. The survival advantage provided by combination chemotherapy over surgery alone has been demonstrated in randomised trials completed in the last decade [66, 70]. As already discussed, pretreatment predictive factors lack the specificity to identify patients who might be treated by surgery alone. Thus, all patients with localised, extremity osteosarcoma should receive chemotherapy although the optimal regimen is as yet undefined. Neoadjuvant

chemotherapy has become accepted practice in the majority of centres using protocols which include the most active agents in this disease, doxorubicin, cisplatin and methotrexate. Newer agents, particularly ifosfamide and etoposide, are increasingly incorporated into complex regimens.

The key unresolved questions in this area include:

- Is there a 'gold standard' chemotherapy regimen for patients with localised extremity disease?
- How should information about histological response be used to adjust treatment?
- What value have newer agents such as etoposide and ifosfamide in the treatment of osteosarcoma?
- Does second-line chemotherapy provide a survival benefit when used in addition to metastasectomy?
- How should patients presenting with metastases be managed?

The T10 protocol devised by Rosen became widely recognised as a highly effective regimen for osteosarcoma [71]. The initial exciting results, reported after a short follow-up, remained impressive when more mature data were published [36]. Other single centres have reported similar figures using either the T10 programme with or without minor variations. The superiority of this regimen over a simple two-drug programme was tested by the European Osteosarcoma Intergroup (EOI) in the largest randomised study conducted in this disease. This study arose after a previous EOI randomised study of nearly 200 patients had failed to demonstrate an advantage for the addition of methotrexate to doxorubicin and cisplatin [72]. This study, although subject to criticism, particularly regarding the dose and schedule of methotrexate used, demonstrated the results achievable in a multicentre setting with a disease-free survival and overall survival in the two-drug arm of 54% and 67%, respectively. In the second EOI study, 407 patients aged up to 40 years were randomised between 1986 and 1991 to receive either 6 cycles of doxorubicin and cisplatin or a 42 week multidrug regimen similar to T10; all patients were treated with cisplatin rather than only those with a poor histological response as in Rosen's original report. The proportion of patients achieving a greater than 90% histological response were 30.3% and 26.8% for the two-drug arm and the multidrug arm, respectively. No difference was evident in this study between the two arms with an overall survival of only 55% at 8 years, disappointing results compared with those being reported from single centres [73]. The two-drug arm is now the reference treatment in a further large EOI randomised study investigating the effect of increasing dose intensity using haematopoietic growth factors [74].

Although now widely practised, it remains unproven that alteration of chemotherapy on the basis of poor histological response can enhance outcome. Data from open and uncontrolled trials may support this notion, but equally other groups have seen no benefit [75–80]. Reasons for this failure might include insufficient initial chemotherapy and ineffective 'salvage' drugs. Furthermore, histological response may be acting as a much more complex surrogate for biological behaviour which is less easily affected by changes in cytotoxic drugs or at least, only becomes evident too late in the time course of the disease. Results of a large randomised study are awaited.

It is only relatively recently that new cytotoxic agents have become available for use in this disease. Ifosfamide is an active agent in sarcomas and other childhood cancers [81]. Single-agent activity has been demonstrated in osteosarcoma [82–84]. Dose escalation up to 14–18 g/m^2 may lead to responses in patients resistant to more conventional doses (6–9 g/m^2) but is associated with more myelosuppression, and acidosis may be severe.

Fewer single-agent data are available for etoposide in osteosarcoma, although once again it has promising activity in other childhood tumours [85, 86]. Interpretation of such data may be misleading as the schedule dependency of etoposide has only been demonstrated more recently [87, 88]. However, in 17 newly diagnosed patients with osteosarcoma, etoposide (600 mg/m^2) in combination with cyclophosphamide (1800 mg/m^2) produced a response rate of 88% [89]. A lower response rate (3/8) has been reported by Miser using ifosfamide (9 g/m^2) and etoposide (500 mg/m^2) in previously treated patients [90]. Norwegian investigators report a response rate of 50% in 16 patients using 4.5 g/m^2 of ifosfamide and a 72 h continuous infusion of etoposide (600 mg/m^2). More recently, the combination of etoposide and carboplatin has shown promising activity in patients previously treated with cisplatin [91].

Carboplatin is an attractive alternative to cisplatin causing less emesis, renal and ototoxicity. Phase I and II studies gave no clear indication of activity due to the inclusion of small numbers of patients with osteosarcoma [92, 93], but a Pediatric Oncology Group study has confirmed only limited activity in previously untreated patients [94]. A small study of paclitaxel has suggested that this agent has no activity, at least in heavily pretreated patients mostly with axial tumours [95]. Results of phase II studies of other new agents such as topotecan and docetaxel are awaited.

Liposomal muramyl tripeptide (MTP-PE) continues to excite interest since the first suggestion of a role in preventing the recurrence of pulmonary metastases. This molecule is a synthesised analogue representing the minimum component of mycobacterium required for stimulating an immune response, and when incorporated into a liposome can localise within the lungs, stimulating the tumoricidal properties of pulmonary macrophages [96]. The results are awaited of a randomised study introducing MTP-PE after standard chemotherapy.

In many solid tumours, promising results are being recorded for poor-risk patients who receive dose-escalated therapy with peripheral stem cell rescue. The major limitation to this approach in osteosarcoma is the absence of active drugs with dose-limiting haematological toxicity. A French group have been encouraged by responses seen after high doses thiotepa but this remains a relatively unexplored area [97].

Pulmonary metastasectomy

Lung metastases were the cause of death in 80% of patients treated by amputation alone, this site being by far the most common site of dissemination of osteosarcoma [98]. Extrapulmonary metastases in the absence of lung disease are rare [99]. Thus, there is a strong rationale for surgical resection of pulmonary metastases and it has long been recognised that this can result in long-term disease-free survival [100], and with aggressive, repeated thoracotomy, perhaps a quarter to a third of patients may survive 5 or more years [101, 102]. More recent studies have concentrated on defining prognostic groupings. Although most reports are retrospective and investigate different criteria, the most powerful favourable

features are unilateral metastases which are few in number (probably less than four), develop at least 18 months after primary therapy and are completely removed preferably with exploration of both lungs [103–111]. Reports of metastasectomy infrequently report the size of the denominator population, but when this is given, it becomes clear that most patients with relapsed osteosarcoma never reach the point of potentially curative surgery [105].

There are no systematic studies of the role of further chemotherapy as part of treatment for pulmonary metastases. Chemotherapy alone has not been reported to produce long-term survival in such patients, but its use in conjunction with surgery has been widely applied [108, 112–114]. Its use before surgery has led to some reports of complete histological response by the time metastatic disease is removed [113]. In one retrospective analysis on 60 patients who developed metastases, treatment with salvage chemotherapy was an independent factor predictive of improved survival [115]. A randomised study is required to answer this question.

Radiation

It is widely held that radiotherapy has only a limited role to play in the management of osteosarcoma, a view often justified using *in vitro* studies of radio-resistance of osteosarcoma cell lines. In the original work of Cade, disease control was achieved by radiotherapy in a few cases [116] and complete necrosis of resected primary tumours has been reported after pre-operative irradiation. The use of radiotherapy differs between centres, for example, in patients deemed at high risk of local recurrence. The advent of bone-seeking radioisotopes which can be used therapeutically may reawaken interest in this modality [117].

Other problems

Patients with extremity lesions in whom lung metastases are detected at the time of diagnosis fare very poorly with currently available treatments [118, 119]. A more aggressive approach to management, for example, intensive chemotherapy followed by simultaneous resection of both primary and metastatic lesions, may salvage some of these patients [120] but new tools are required. Patients who present with or develop bone metastases are very rarely cured [121]. Pelvic and vertebral osteosarcomas are rare, particularly in children, often present late and usually defy satisfactory treatment with resistance to chemotherapy common and resection difficult or impossible [122–125]. Again, novel treatment methods are justified.

CONCLUSION

The major problems facing investigators over the next 5 years include the accurate identification of those most likely to be cured with available treatments and particularly that small group who may be cured with a minimum of intervention. There will remain perhaps 40% of patients for whom little chance of cure can be expected and it is in that group that we must await major biological insights to guide new therapeutic intervention. Much of the initial progress towards cure of this disease came from far-sighted investigators in specialist hospitals with unique referral practices. To make further inroads against osteosarcoma may require us to enter a new era of international collaboration to assess the strength of biological observations and to test new therapeutic strategies in large groups of patients. In the meantime, those diagnosed with this rare and challenging disease, particularly adolescents, deserve the experience and multidisciplinary care available only in specialist centres.

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Commentary

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THE OUTCOME for 'classic' high grade osteosarcoma of extremities has improved dramatically over the past 25 years. Limb salvage surgery is widely used, employing metal protheses or allografts, although in his update (pp. 1611–1619) Dr Whelan is right to highlight concerns about their durability in young active individuals. In addition, the less widely used Van Ness procedure, which converts an above knee to a below knee amputation, provides an excellent functional outcome in selected patients willing to tolerate the unusual appearance.

The relative merits of randomised controlled trials (RCTs) versus innovative pilot studies is particularly hotly debated in the setting of adjuvant chemotherapy for osteosarcoma. I feel that both types of studies are important, but that certain questions can only be answered by RCTs. Unfortunately results of some RCTs have been inconclusive because of inadequate size. Dr Whelan outlines some key unresolved issues regarding adjuvant chemotherapy, and these can best be addressed in RCTs. However, the logistics of performing such studies in this rare tumour are formidable and would need not only multi-centre but multi-cooperative group collaboration.

The relationship between a 'good response' (histopathological necrosis $\geq 90\%$) after neoadjuvant chemotherapy and outcome is convincing, based on several reported studies. However, the percentage of tumours showing a 'good response' ranged from 27–41% in the three studies shown in Table 1 of Dr Whelan's update. The group from the Memorial Sloan Kettering Center, U.S.A. [1] found that longer pre-operative treatments produced higher rates of histological response, but the correlation with outcome decreased. More recent studies, using dose intensive multi-agent regimens, including ifosfamide, have shown 'good responses' in 72–87% of patients [2, 3]. When survival data are available from these studies it will be interesting to see if histological response is still of prognostic importance.

Necrosis after chemotherapy, similar to that seen in the primary tumour, also occurs in pulmonary metastases, as illustrated by two series of patients from Bologna, each comprising 23 patients with synchronous primary tumours and pulmonary metastases, treated with neoadjuvant chemotherapy between 1983–1989 [4] and 1993–1995 [5]. The latter cohort received pre-operative ifosfamide in addition to high dose methotrexate/cisplatin/doxorubicin. 'Good responses' were more frequent both in primary tumours (73 versus 26%) and in metastases (89 versus 24%) in the second series and there was a better correlation, within patients, of histopathological response between primary and metastases.

As noted by Dr Whelan, a Pediatric Oncology Group randomised trial showed no survival disadvantage for