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Dedifferentiated chondrosarcoma: Prognostic factors and outcome from a European group

Robert J. Grimer[a,*], *Georg Gosheger*[b], *Antonie Taminiau*[c], *David Biau*[d], *Zdenek Matejovsky*[e], *Yehuda Kollender*[f], *Mikel San-Julian*[g], *Franco Gherlinzoni*[h], *Cristina Ferrari*[i]

[a]*Royal Orthopaedic Hospital, Bristol Road South, Birmingham B31 2AP, UK*
[b]*University of Muenster, Albert Schweitzerstrasse 33, Muenster, D-48129, Germany*
[c]*Leiden University Medical Centre, PO Box 9600, Leiden 2300RC, The Netherlands*
[d]*Hôpital Cochin, 27 rue duFabourg Saint-Jacques, 75679, Paris CEDEX 14, France*
[e]*Orthopedic Clinic Bulkova, Ist Medical School Charles University, Budinova 2, Prague 8, Czech Republic*
[f]*Tel-Aviv Sourasky Medical Centre, 6 Weizman Street, Tel Aviv 64239, Israel*
[g]*University of Navarra, Avda P10 XII, 36, Pamplona 31008, Spain*
[h]*Gorizia General Hospital, Gorizia 34170, Italy*
[i]*Istituto Ortopedico Rizzoli, Labratory of Oncologic Research, Via Pupilli 1, Bologna, 40136, Italy*

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ABSTRACT

Background: Dedifferentiated chondrosarcoma has a very poor prognosis. Because of its rarity, there are few large studies of outcome which might identify potential prognostic factors. In particular there remains uncertainty about the value of chemotherapy for this condition.

Method: A retrospective study was done using data supplied by members of the European Musculo Skeletal Oncology Society (EMSOS). We obtained data on 337 patients from nine European centres with this rare condition, with details on patients, treatment and outcome which were then analysed in an attempt to identify prognostic features.

Results: The median age was 59 years and there was a slight predominance of males (53%). The most common sites were the femur and pelvis. Twenty-nine percent of patients with a long bone tumour had a pathological fracture. 71 patients (21%) had metastases at the time of diagnosis and these patients had a median survival of 5 months with a 10% chance of survival at 2 years. For the 266 patients without metastases at diagnosis, 254 underwent surgery with 79% having limb salvage. Thirty-one percent of these 266 patients had chemotherapy with 47% of those under 60 receiving it. In this group of 266 patients, overall survival was 28% at 10 years and poor prognostic factors were the presence of a pathological fracture at diagnosis, a pelvic location and increasing age. Local recurrence and overall survival were related to inadequate margins of excision. We did not find that the histological subtype, size of the tumour or the use of chemotherapy significantly affected outcome. For all patients the overall survival was 24% at 5 years.

Conclusions: The prognosis for patients with dedifferentiated chondrosarcoma remains dismal. Surgery with clear margins remains the principal treatment for this condition. Further use of chemotherapy should be within a trial or treatment protocol.

* *Corresponding author:* Tel.: +44 121 685 4150; fax: +44 121 685 4146.
E-mail address: Rob.Grimer@roh.nhs.uk (R.J. Grimer).
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1. Introduction

Dedifferentiated chondrosarcoma is a relatively rare variant of chondrosarcoma, arising in between 10% and 15% of all chondrosarcomas.[1] Unlike most chondrosarcomas, the dedifferentiated variety are high grade malignant tumours with a typical bimorphic histological appearance with areas of a lower grade chondrosarcoma adjacent to a high grade sarcoma. The high grade tumour can be either an osteosarcoma, a malignant fibrous histiocytoma or an anaplastic spindle cell sarcoma. First described by Dahlin and Beabout in 1971,[2] there have been few large series of this rare tumour reported. Until recently, the overwhelming theme of these reports was the dismal prognosis of patients with this tumour and the failure of treatment to improve outcome.[3–7]

With the advent of chemotherapy for bone sarcomas, there was a natural tendency to explore the role of chemotherapy in younger patients with dedifferentiated chondrosarcoma. A report from Mitchell et al. in 2000[5] suggested improved survival in those patients receiving chemotherapy but subsequent papers have failed to confirm this,[6,8] although the most recent paper by Staals et al. has shown improved survival of 24% at 5 years, even though this did not appear to be due to the effect of chemotherapy.[9] None of the papers documenting the use of chemotherapy reported many cases with a good histological response to neoadjuvant treatment with Staals et al. having no good responders in four patients.[9] Mitchell et al. having one out of 5 good responders,[5] and Dickey et al. reporting the presence of little necrosis suggesting a poor chemotherapy response in their 21 patients who received neoadjuvant chemotherapy.[7]

The purpose of this paper was to use an existing network of orthopaedic oncology centres, all members of the European Musculo Skeletal Oncology Society (EMSOS) and a past history of collaborative studies[10,11] to produce a large dataset of patients with dedifferentiated chondrosarcoma to identify prognostic factors and in particular to assess whether we could identify any beneficial effect of chemotherapy.

2. Method

The project was formulated and discussed at the EMSOS annual meeting held in Trieste in 2005. The senior author produced a questionnaire which was discussed and modified by members of the group and was subsequently circulated to all members of EMSOS, inviting them to collaborate. Details about the patient, the tumour, the treatment and the outcome were requested. It was accepted that we would have to rely upon the local expertise of surgeons, radiologists and pathologists to make the diagnosis and no attempt was made to centrally review either the radiology or the histology. Previous studies carried out by us had shown the complete futility of trying to do this in a retrospective multicentre study.[10,11] Patients who had undergone treatment at more than one centre were identified by checking their date of birth and tumour details and when necessary, information from the two centres was amalgamated for the final record. Patients with incomplete data entry were included in subsequent analysis of tumour and patient characteristics if possible but were excluded from the analysis of prognosis if either treatment or outcome data were insufficient.

Because of the rarity of this condition we accepted that some of the patients in this study will have been included in previous analyses, but all the follow-up data were updated for the purposes of this analysis.

Survival time was taken from the date of diagnosis to the last date when the patient was documented to be alive or the date of death. Differences between groups were analysed using the χ^2 test for discrete variables or the use of the two sample t-test or Mann–Whitney test for continuous variables. Survival analysis was done using Kaplan–Meier survivorship. The Cox proportional hazards regression model was used to assess the effect (hazard ratio (HR)) on the primary outcome of age at diagnosis, location of tumour (central versus peripheral), presentation with a pathologic fracture (yes versus no), type of surgery (limb salvage versus amputation), adequate margins achieved (yes versus no), and chemotherapy (yes versus no). Only patients likely to be cured, i.e. those who had no metastases at diagnosis and who underwent surgical treatment were studied ($n = 254$ patients).

The proportional hazards assumptions were checked with the use of time-varying coefficients and the linear effect of age (as a continuous variable) was assessed with splines. A multivariable analysis with a backward stepwise variable selection procedure, based on Akaike's information criterion,[12] was used to identify the set of independent predictors of treatment failure.

For quantitative variables (continuous variables), we report the median, first and third quartile values. Categorical variables are reported as counts. All analyses were performed with *R* statistical software[13] and Statwiew.[14] All tests were two sided, with a significant level of 0.05.

When patients were grouped for more detailed analysis this has been clearly specified in the text and the results.

3. Results

Nine centres in eight different countries contributed data, resulting in a total of 337 patients on whom there was enough data for all or some of the analyses. The largest problem was with the lack of follow-up, particularly in patients with metastatic disease who were often referred for palliative care but in whom there was not always a date of death available. They were censored at the date of last follow-up. The patients were registered at the various centres between 1975 and 2005 with a maximum of 20 new cases per year being reported.

Fifty-three percent were male and 47% female and the median age was 59 years (range of 15–89 years) (Fig. 1). The tumour involved the femur in 154 patients (46%), the pelvis in 95 (28%), the humerus in 37 (11%) the scapula in 18 (5%) and 33 in other locations. 233 of the tumours involved long bones of the peripheral skeleton whilst 104 involved the axial skeleton (pelvis, rib, etc.). 71 patients (21%) had metastases at diagnosis and 71 patients (21%) had a pathological fracture at the time of diagnosis. Only 2 patients (2%) with axial tumours suffered from fractures but 69 of the 233 patients (29%) with a long bone location had a fracture ($p < 0.0001$). There was no relationship between the incidence of metastases at diagnosis and of fracture.

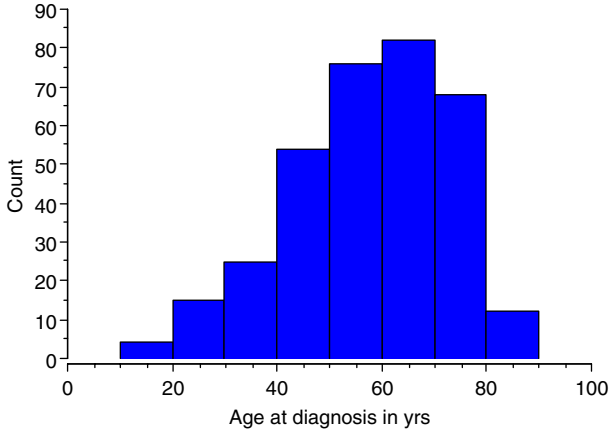

Fig. 1 – The age distribution of the 337 patients.

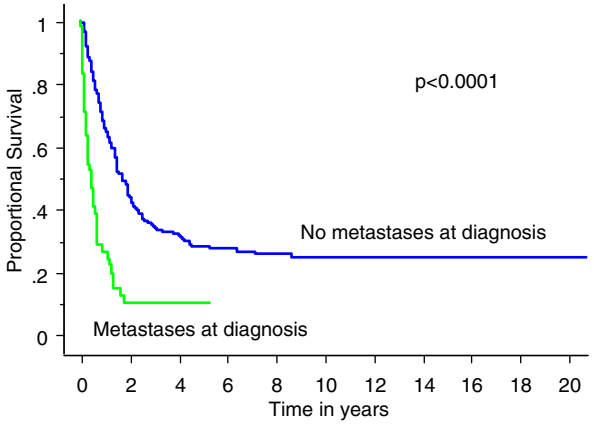

Fig. 2 – Kaplan–Meier survival curve for the overall survival of all patients with evaluable data comparing those with metastases (n = 62) and without metastases (n = 242) at diagnosis.

The size of the tumour at diagnosis averaged 12.6 cm (range of 4–25 cm) but was only available for 76 cases. The grade of the underlying cartilage tumour was documented in 199 patients and was grade 1 (low grade) in 61(31%), grade 2 in 81 (41%) and grade 3 (high grade) in 57 (28%). The type of spindle cell tumour was reported in 292 patients and was osteosarcoma in 104 (31%), spindle cell sarcoma in 82 (24%), MFH in 73 (22%) and fibrosarcoma in 24 (7%). There was no relationship between the grade of the underlying cartilage tumour and the type of dedifferentiated component.

Many patients had the tumour diagnosed unexpectedly following either curettage or following resection of what was thought to be a low grade chondrosarcoma. We could find no evidence that diagnosis prior to treatment affected outcome although it did give the opportunity for the patient to have neoadjuvant chemotherapy in some cases.

The overall survival rates for all patients were 59% (±5.7%) at 1 year, 38% (± 5.9%) at 2 years and 24% (±5.5%) at 5 years. Median survival for all patients was 1.4 years.

4. Patients with metastases at diagnosis

71 patients presented with metastases at the time of diagnosis. The patients were of similar age and their tumours were of similar size to those without metastases. Of the 71 patients, 18 simply received supportive treatment and 8 had palliative chemotherapy. 45 underwent surgical excision of the tumour (18 with an amputation and 27 with limb salvage) and of these, 9 also had chemotherapy. Only one patient had assessment of chemotherapy response following neoadjuvant chemotherapy and surgical excision and the necrosis was 75%. Details of the chemotherapy response were not available for other patients.

The median survival for the patients who presented with metastases was 5 months with 26% being alive at 1 year and 10% at 2 years following diagnosis (Fig. 2). Although not statistically significant there was a trend for patients who underwent more aggressive treatment (surgery and chemotherapy) to live slightly longer (7 months versus 3 months for those without any treatment), although this difference is likely to be more of a reflection of the patients general condition at the time of diagnosis rather than of the effectiveness of treatment. There were no survivors documented beyond 5 years from the date of diagnosis in those with metastases at the time of diagnosis.

5. Patients without metastases at diagnosis

266 patients did not have identifiable metastases at the time of diagnosis and were thus considered potentially curable. 254 of them underwent surgical excision of the tumour, 56 by amputation (21%) and 198 with limb salvage (79%). Of the remaining 12 patients, 2 progressed on chemotherapy and 10 had palliative treatment, usually with radiotherapy either because of the extent of the tumour or comorbidity preventing other treatment. Limb salvage was carried out in 35 of the 50 patients (70%) in the group with a pathological fracture whilst amputation was needed in 12 (24%) and 3 had no operation. This contrasted with limb salvage being achieved in 75% of those without a pathological fracture.

A total of 81 patients in the group of 266 (31%) had chemotherapy, of whom only 25 had neoadjvant chemotherapy and the remainder adjuvant. There were a wide range of drug regimes used, the most common being a combination of doxorubicin and cisplatin used in 30 patients, whilst the combination of doxorubicin and ifosfamide was used in 10 patients. Five patients had methotrexate in addition to doxorubicin and cisplatin but in the remainder the actual regimes or drugs used were not specified.

Chemotherapy was used in 67 of the 141 (47%) patients ($p < 0.0001$) up to the age of 60 and in 14 of the 124 older than 60 (11%). 16 of the 56 patients (28%) who had an amputation received chemotherapy as did 63 of the 198 undergoing limb salvage (32%).

Of the 25 patients who received neoadjuvant chemotherapy, assessment of response was only available for 13, of whom one had complete necrosis of the tumour and one 90% necrosis. The others all had less than 90% necrosis with 7 having less than 50% necrosis. There was thus only one good response in 2/13 cases (15%). There was no obvious difference in outcome based on the regime of drugs used.

198 patients underwent limb salvage, 56 had an amputation and 12 did not have an operation (either because of the location of the tumour or due to progressive disease). The rate of amputation was 12 out of 47 in patients with a pathological fracture (26%) and was 44 out of 207 (21%) without a fracture ($p = 0.52$). The surgical margins achieved were classified in 237 of the 254 who underwent surgery. 174 (73%) had wide or radical margins (classified as adequate), whilst 63 (27%) were felt to have marginal or intralesional excisions (classified as inadequate). Inadequate margins were obtained in 32% of those undergoing limb salvage compared with 9% of those having amputations. There was a slight apparent increase in inadequate margins in patients with axial as opposed to limb tumours (32% versus 23%) ($p = 0.0163$) but the presence of a pathological fracture did not increase the risk of inadequate margins being reported versus those without a fracture (26% versus 25%, respectively, $p = 0.55$).

In the 254 patients who had an operation, 41 developed a local recurrence (16%). Local recurrence was related to the margins of excision, with a 11% rate in patients with an adequate excision and 29% rate in those with inadequate excision ($p = 0.0016$ χ^2 test). There was no increased risk of local recurrence in patients with pathological fractures, axial tumours or in those undergoing limb salvage compared to amputation. Kaplan–Meier analysis revealed a 12% risk of local recurrence at 2 years for those with adequate margins, but 36% for those with inadequate margins.

Of the group of 266 patients without metastases at diagnosis, 242 had sufficient data for survival analysis. Overall survival revealed a 1 year survival of 66% (±6%), a 2 year survival of 44% (±6.4%), a 5 year survival of 28% (±6.5%) and a 10 year survival of 24% (±6.5%) (Fig. 2). Table 1 shows univariate risk factors affecting survival with hazard ratios. There was no difference in survival based on gender, site, histological subtype, size or margins of surgical excision. The presence of a pathological fracture was the most significant poor prognostic factor and that patients who required amputation did badly, presumably because these patients are likely to have extensive tumours. There was a trend for younger patients to do slightly better but there was no obvious improvement in survival with the decade of treatment. The multivariate final model selected the following variables as significantly predictive of death: older age at diagnosis ($p = 0.0024$), axial location of tumour ($p = 0.016$), presentation with a pathologic fracture ($p = 0.0019$), and involved margins of resection ($p = 0.0034$). Hazard ratios are presented in Table 2.

Investigating just the 98 patients who were under the age of 60 at the time of diagnosis and who had limb salvage surgery (i.e. a group who had operable tumours and who could potentially receive meaningful chemotherapy), we found that

Table 1 – Factors that affected survival in the patients who were considered potentially curable at the time of diagnosis (i.e. did not have metastases, n = 242)

Factor	Number evaluable	Five year survival (%)	Hazard ratio (confidence intervals)	p Value
All patients	242	28		
Location				
Axial	73	20	1.239 (0.888–1.27)	0.207
Limb	169	31	1	
Pathological fracture				
Fracture	41	15	1.81 (1.214–2.7)	0.0036
No fracture	201	30	1	
Surgery				
None	7	0	1	
Amputation	53	19	0.284 (0.119–0.679)	0.0047
Limb Salvage	182	32	0.197 (0.085–0.457)	0.0002
Margins achieved				
Adequate	159	31	1	
Inadequate (no data for 21 patients)	62	24	1.327 (2.071–11.074)	0.123
Age				
Under 60	128	32	1	
Over 60	114	22	1.339 (0.978–1.832)	0.0688
Chemotherapy				
Yes	76	33	1.317 (0.931–1.86)	
No	166	25		0.1192
Age as continuous variable			1.014 (1.003–1.024)	0.0124
Decade of diagnosis				
1970s	7	28		
1980s	63	23		NS
1990s	109	29		
2000	63	34% at 4 years		

Table 2 – Final multivariate model with backward stepwise selection procedure based on Akaike information criterion

Variables	HR (95% CI)	*p* Value
Location (peripheral)	0.59 (0.38–0.91)	0.016
Pathological fracture (yes)	2.04 (1.30–3.19)	0.0019
Clear margins achieved (yes)	0.55 (0.37–0.82)	0.0034
Age	1.02 (1.01–1.04)	0.0024

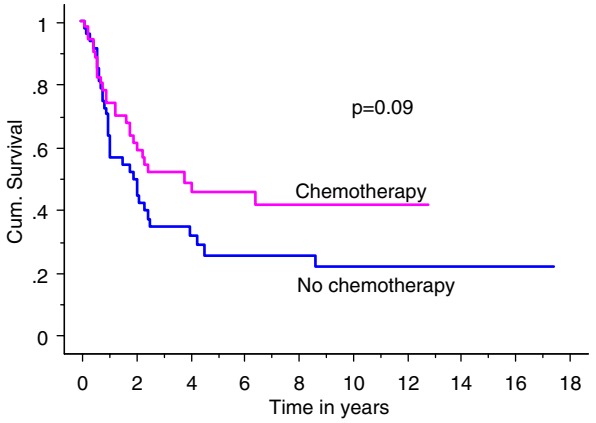

Fig. 3 – Kaplan–Meier curves showing overall survival in patients aged under 60 without metastases at diagnosis who had limb salvage, split by whether they had chemotherapy or not. The difference is not significant ($p = 0.09$).

51 had chemotherapy and 47 did not. The 5 year survival was 25% (±13.7%) in those who did not have chemotherapy compared with 45% (±15%) in those who did but this was not significant on univariate analysis (HR 1.55 (confidence interval (CI) 0.927–2.597)) ($p = 0.09$) (Fig. 3).

Radiotherapy was documented to have been used in 35 patients, in some for palliation, in some for the involved margins of excision and in some for the management of local recurrence but it was impossible to identify what benefit this produced.

6. Discussion

Dedifferentiated chondrosarcoma is a tumour with a fearful reputation. Up until 2000, the reported results were so bad that no author had obtained more than 20% at 5 year survival (Table 3) and the usual recommendation was to excise the tumour with wide margins or even with amputation.[1] Given this appalling prognosis it is not surprising that attempts have been made to control the tumour with chemotherapy. The cause of the poor prognosis is presumably the high grade spindle cell component of the tumour but experience of outcomes in similar aged patients both with osteosarcoma and spindle cell sarcomas who received chemotherapy would suggest 5 year survival rates of between 46% and 59% could be obtained.[11,15]

The reason why these survival figures have not been matched by the use of chemotherapy remains an enigma. We have not shown any difference in outcome between the different histological subtypes, unlike the study of Staals et al. who suggested that patients with a malignant fibrous histiocytoma high grade component do worst.[9] In that study, a definitive review of the histological nature of the tumours was carried out but this was not systematically done for this study. They also found that patients with a high percentage of dedifferentiated component did worst, but again we were unable to measure this on such a large retrospective series from many different centres.

Table 3 – Details of survivorship for all presenting patients taken from key papers over the past 20 years

Author	Year	Number	Two year survival (%)	Five year survival (%)
Frassica et al.[3]	1986	78		10.5
Capanna et al.[4]	1988	46	6	6
Mercuri et al.[5]	1995	74		13
Mitchell et al.[6]	2000	22		18
Dickey et al.[7]	2004	37	20	7
Bruns et al.[8]	2005	13		8
Staals et al.[9]	2006	123	34	24
Staals et al.[18]	2007	18	47	29
This study	2007	337	38	24

We have, however, confirmed the finding of others that patients with metastatic disease at presentation have a very poor outlook and although this may be improved slightly by surgery, other palliative measures such as chemotherapy have not been shown to improve the outcome.

The results presented here are very similar to those of Staals et al. but Staals series included patients treated as long ago as 1969, in an era that not only predated Dahlin's description of the disease but also predated modern methods of staging, surgery and chemotherapy. The patients in our series were diagnosed from 1975 onwards but we were unable to show that the decade of treatment made any difference to the outcome whatsoever. This would certainly suggest that the natural history of the disease has not been greatly influenced by improvements in staging the disease (e.g. computed tomography (CT) scans to identify those with metastases earlier) or the advent of limb salvage surgery. We did note, however, that there was a greater tendency to offer limb salvage as opposed to amputation with the passage of time.

We have been unable to show that treatment significantly affected survival although obtaining clear margins of excision improved local control. Although 47% of all the patients under 60 without metastases at diagnosis had chemotherapy, the improvement in survival obtained did not reach significance. It is possible that this is indeed because chemotherapy has little effect in this condition and this would be supported by the low response rate in the patients who received neoadjuvant chemotherapy. This would also suggest that complete surgical excision should be the initial treatment for all patients with a dedifferentiated chondrosarcoma and that chemotherapy, if it is used, should be considered as an adjuvant. More intensive regimes of chemotherapy, which are now becoming more commonplace for osteosarcoma and for spindle cell sarcomas (cf. EURAMOS[16] and EUROBOSS[17]) may yet be shown to

have a role in improving outcome in this condition, particularly in patients who can tolerate a full dose of treatment, usually those under the age of 60. Given the lack of convincing evidence of benefit of chemotherapy in this condition and the toxicity of chemotherapy regimes especially in older patients, we do not consider that chemotherapy can be considered as a standard treatment outwith a trial setting.

Explaining why there have been improvements in outcome compared to previous papers is thus probably based on a slow trend for improved outcomes with time, possibly due to earlier diagnosis, improved staging or more aggressive treatment, both of the primary and possibly of metastatic disease, although these hypotheses would be difficult to prove. There is also a possibility of selection bias of patients included in this retrospective study by the various institutions although we specifically requested details of all patients with this diagnosis from the contributing centres.

With a retrospective, multi-institutional study like this there will always be major weaknesses in that data cannot be corroborated and complete reliance is based on the accuracy of the reporting unit's data. Whilst this could potentially lead to errors both in diagnosis and outcome analysis we do not believe that the effect will be significant, given the national and international reputations of the units which supplied data for this study. We also did not split the tumours into whether they were central or peripheral, although a recent work by Staals et al. has shown no difference in survival between those patients with central dedifferentiated chondrosarcomas and those arising in osteochondromas.[18]

7. Conclusion

In conclusion, we have confirmed that dedifferentiated chondrosarcoma has one of the worst outlooks of any primary malignant bone tumour. Patients with metastases have a particularly poor prognosis as do those with a pathological fracture at the time of presentation.

We would recommend that any chondroid tumour showing features of aggressive bone destruction should be investigated to try and lead to earlier diagnosis. In patients found to have a dedifferentiated chondrosarcoma complete surgical excision should be attempted primarily and patients should ideally be considered for a standardised form of adjuvant chemotherapy as part of a prospective international study. At the present time, the EUROBOSS study[17] will allow the registration of patients with dedifferentiated chondrosarcomas between the age of 41 and 65 and has the advantage of specific recommendations about treatment with chemotherapy using combination chemotherapy with ifosfamide, adriamycin and cisplatin with the addition of methotrexate for those with a poor response to neoadjuvant therapy. This trial should produce a large cohort of patients undergoing similar treatment and we would urge the members of EMSOS to enter their patients into this prospective cohort study.

Conflict of interest statement

None of the authors have any financial or other personal interest associated with publication of this article.

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