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A Novel System for the Surgical Staging of Primary High-Grade Osteosarcoma: The Birmingham Classification

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Background

The development of local recurrence is associated with a poor prognosis in high-grade osteosarcoma. Factors associated with the development of local recurrence include a poor response to neo-adjuvant chemotherapy and an inadequate surgical margin. While the relationship between inadequate margins and LR has been demonstrated, there remains significant debate as to what constitutes an adequate margin. The most commonly reported staging system is the Musculoskeletal Tumor Society (MSTS) system introduced by Enneking et al. in 1980[7]. Most papers identify an adequate margin as either *wide* or *radical* by Enneking's criteria, and an inadequate margin as *intralesional* or *marginal*. The interpretation of what exactly constitutes a marginal and wide excision is often subjective and may vary depending on the reporter. The advent of modern chemotherapeutic regimens, which postdate the proposal of Enneking's criteria, have significantly improved overall and disease free survival for patients with osteosarcoma[9]. The impact of a poor tumour response to ne-adjuvant chemotherapy is translated as an increased of LR. Arguably, a poor response to chemotherapy (<90% necrosis) is the now the most important risk factor for LR. Given that existing staging systems fail to reflect this or provide the surgeon with an adequate metric distance for safe excision, there is a need for an updated staging system that addresses both of these aspects.

Purposes

The aim of this study was to identify the safe surgical margin for resection of high-grade osteosarcomas of bone. Having identified this margin, we have then developed a novel staging system (the Birmingham Classification) incorporating both margin and tumour response to neo-adjuvant chemotherapy.

Patients and Methods

All patients with a histologically proven high-grade osteosarcoma of bone treated at a single institution were identified from the unit's prospectively maintained database which records all patient interactions at the unit. Inclusion criteria from this population included age (0-49) and time of presentation (1st January, 1997-31st December, 2012). Only patients who were treated with neo-adjuvant chemotherapy (as per national and international protocols) and surgical resection were included. Univariate and multivariate regression analysis was used to identify factors predictive of LR. On the basis of these findings, the Birmingham Classification was proposed. This comprises 2 stems governed by the response to chemotherapy (good response = ≥ 90% necrosis; poor response = <90% necrosis) with 2 subdivisions within each stem (margin >2 mm or margin ≥ 2mm). To assess the efficacy of the novel staging system at predicting LR free survival, a two-stage Cox regression model incorporating both the existing MSTS staging criteria and the novel Birmingham Classification was undertaken and Harrell's C statistics calculated. Median duration of follow up was 57 months.

Results

The population comprised 389 patients. The demographics of the study population are shown in Table 1. Endo-prosthetic reconstruction was carried out in 70.7%, with amputation in 23.1%, excision without reconstruction in 2.8%, reconstruction with allograft in 2.8% and rotationplasty in 0.5%. 41.8% had a good response to neo-adjuvant chemotherapy. A poor response to chemotherapy increased the likelihood of local recurrence fourfold from 4.6% to 17.6%. (HR 4.10, P<0.001).

The overall incidence of LR was 12.1%. This was highest in patients who had an excision (18.2%), followed by those treated with an EPR (14.0%), and lowest in those treated by amputations (5.6%). Significant univariate predictors of local recurrence were pelvic tumour location (41.7%, HR 5.31, P=0.008) and vascular invasion (25.0% vs 10.6%, HR 2.82, P=0.008).

According to the Birmingham Classification (Table 2), the incidence of LR for each group was: 1a (1.5%, P=0.007), 1b (7.4%, HR 5.66, P=0.117), 2a (12.0%, HR 9.67, P=0.029), and 2b (22.5%, HR 17.34, P=0.008). According to the MSTS criteria the incidence of LR when stratified by margin was: radical (2.4%, P=0.258), wide (11.2%, HR 5.69, P=0.095), marginal (13.8%, HR 3.97, P=0.220), intralesional (26.1%, HR 6.16, P=0.126).

Table 2 shows the Cox regression model where the MSTS criteria were entered into the first stage and the Birmingham Classification into the second stage. The regression model would only permit this if the introduction of the latter significantly improved the prediction of LR above the MSTS criteria alone. The Harrell's C statistic was 0.591 for the MSTS criteria and 0.676 for the Birmingham Classification.

Conclusion

This large, observational study demonstrates a comparable incidence of LR to previous studies. It confirms that both response to chemotherapy and the surgical margin are strongly predictive of LR. In addition, it has identified vascular invasion and pelvic tumour location as important risk factors for the development of LR.

The results of the two-stage Cox regression and higher Harrell's C statistic demonstrates that the Birmingham Classification is more predictive of the development of LR when compared to the MSTS criteria. The recording of surgical margins in millimetres and the response to neo-adjuvant chemotherapy is now standard practice in the majority of centres treating patients with osteosarcomas of bone. We propose that the adoption of such a system incorporating these variables will allow standardisation of treatment and monitoring as well as improve the comparison of cases and aid future research. Given that this system was devised from retrospective data, a large prospective validation of the Birmingham Classification is needed.

References

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Table 1: Participant demographics and univariate hazard ratios for local recurrence								
		Number	**Percentage**	**Number of LR**	**LR incidence**	**P-Value**	**Hazard Ratio**	**95% CI**
Gender	Male	228	58.6%	24	10.6%	0.258	1.42	0.77-2.62
	Female	161	41.4%	23	14.5%			
Age (years)	<16	218	56.0%	32	14.9%	0.074	1.80	0.94-3.46
	≥16	171	44.0%	15	8.8%			
Tumour Location	Femur	196	50.4%	23	11.9%	0.225		
	Tibia	99	25.4%	8	8.2%	0.336	0.66	0.28-1.54
	Humerus	51	13.1%	9	18.0%	0.255	1.63	0.70-3.79
	Fibula	23	5.9%	1	4.3%	0.300	0.338	0.04-2.63
	Pelvis	12	3.1%	5	41.7%	0.008	5.31	1.56-18.12
	Radius	3	0.8%	0	0%	1.000	0.00	-
	Ulna	2	0.5%	0	0%	1.000	0.00	-
	Calcaneum	1	0.3%	0	0%	1.000	0.00	-
	Scapula	1	0.3%	1	100%	1.000	1.2^{10}	-
	Talus	1	0.3%	0	0%	1.000	0.00	-
Type of Operation	Endoprosthetic Reconstruction	276	71.0%	39	14.3%	0.320		
	Amputation	89	22.9%	5	5.7%	0.039	0.36	0.14-0.95
	Allograft	11	2.8%	1	9.1%	0.631	0.60	0.08-4.82

	Excision	11	2.8%	2	18.2%	0.719	1.33	0.29-6.40
	Rotationplasty	2	0.5%	0	0%	1.000	0.00	-
Fletcher's Sub-classification of Osteosarcoma	Osteoblastic	199	51.2%	23	11.7%	0.803		
	Chondroblastic	34	8.7%	7	21.2%	0.138	2.04	0.80-5.22
	Telangiectatic	26	6.7%	3	11.5%	0.881	0.89	0.19-4.10
	Fibroblastic	19	4.9%	2	10.5%	0.98	0.99	0.28-3.55
	Giant Cell	4	1.0%	0	0%	1.000	0.00	-
	Small Cell	3	0.8%	1	33.3%	0.285	3.78	0.33-43.38
	Mixed	46	11.8%	5	11.1%	0.915	0.95	0.34-2.26
	Unclassified	58	14.9%	6	10.3%	0.779	0.87	0.34-2.26
Intra/extra-compartmental	Intra-compartmental (IIa)	119	30.8%	13	10.9%	0.581	1.21	0.61-2.40
	Extra-compartmental (IIb)	267	69.2%	34	12.7%			
	Missing	3						
Pathological Fracture	Yes	74	19.0%	4	5.4%	0.056	0.36	0.12-1.03
	No	315	81.0%	43	13.8%			
Skip Lesions	Yes	8	2.1%	1	14.3%	0.866	1.20	0.14-10.22
	No	381	97.9%	46	12.2%			
Vascular Invasion	Yes	44	11.3%	11	25.0%	0.008	2.82	1.31-6.07
	No	345	88.7%	36	10.6%			

Total		**389**		**47**	**12.1%**			

Table 2: Two stage Cox regression demonstrating the ability of the MSTS staging system and the Birmingham Classification to predict local recurrence

		Number	Percentage	Number of LR	LR incidence	P-Value	Hazard Ratio	95% CI
MSTS Stage	**Intralesional**	24	6.2%	6	26.1%	0.126	6.16	0.60-63.18
	Marginal	176	45.7%	24	13.8%	0.220	3.97	0.44-35.85
	Wide	143	37.1%	16	11.2%	0.095	5.69	0.74-43.89
	Radical	42	10.9%	1	2.4%	0.258		
	Missing	1						
Birmingham Classification Margin Status	**M1a: Necrosis ≥ 90% and margins > 2mm**	68	17.8%	1	1.5%	0.007		
	M1b: Necrosis ≥ 90% and margins ≤ 2mm	89	23.3%	7	7.9%	0.117	5.66	0.65 - 49.54
	M2a: Necrosis < 90% and margins > 2mm	100	26.2%	12	12.0%	0.029	9.67	1.26 – 74.52
	M2b: Necrosis < 90% and margins ≤ 2mm	120	31.4%	27	22.5%	0.008	17.34	2.10 – 143.12
Total		**389**		47				