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Prognostic Factors Affecting Management of Liposarcoma

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Prognostic Factors Affecting Management of Liposarcoma

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I. Introduction

Liposarcoma is the most common histology of soft tissue sarcomas accounting for approximately 20 to 30% of all sarcomas in adults [1, 2]. Despite soft tissue and skeletal tissue being the most abundant tissue in the body, soft tissue sarcomas accounts for 1% of neoplasms [3, 4]. Prognostic features and subsequent clinical behaviour of soft tissue sarcoma are said to be associated with histology and anatomical distribution [3]. These tumours often grow to large sizes, thus their management presents major challenges [4]. The following case is presented to discuss the prognostic factors affecting the clinical behaviour of liposarcoma post limb sparing surgery.

II. Case Presentation

A 48 year old male presented to the Orthopaedic outpatient clinic with a one year history of a painless mass in the back of the right knee. This mass gradually increased in size. There was no history of numbness or weakness in the right lower limb. He denied having constitutional symptoms.

On examination, mucous membranes were pink, moist and anicteric. There was no lymphadenopathy. Significant findings were confined to the right lower limb where there was a large ill defined mass centred over the popliteal fossa. The mass was approximately 14cm by 7cm. The mass was firm, nontender, nonpulsatile, normal temperature, not attached to skin or muscle. There were no distal neurovascular deficits. CT of the chest, abdomen and pelvis were normal. MRI showed a large heterogeneous fatty mass surrounded by, but not arising from muscle measuring 24 cm by 12 cm by 8 cm. The mass was confined to the posterior compartment of the thigh and popliteal fossa but did not invade the knee joint. Two open biopsies returned an inconclusive result. In consultation with the patient, a wide local excision of the mass was performed (see Figures 1 and 2).

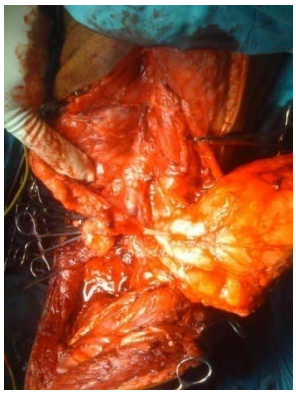

Fig. 1

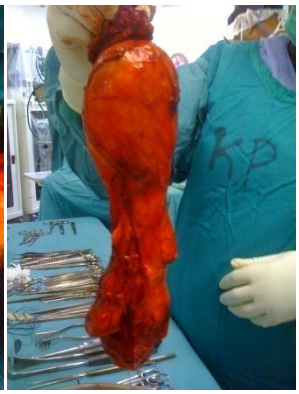

Fig. 2

Histology of the excision revealed a well differentiated liposarcoma with microscopic involvement of one of the surgical margins. The Oncologists deemed it unnecessary to offer chemotherapy. The offer of radiotherapy was turned down by the patient because he was unwilling to face the potential complications of this treatment. At two years follow-up, he had shown no clinical evidence of recurrence locally or by metastasis. He was however unable to afford an MRI or CT to allow for radiological assessment of recurrence.

III. Discussion

Soft tissue sarcomas are heterogeneous, malignant tumours [5, 6]. In relation to other types of cancer they are relatively rare where 5000 new cases are diagnosed yearly [7], representing about 1% of all newly diagnosed neoplasms [8, 9]. Liposarcoma constitutes about 9 to 18% of all soft tissue sarcomas, second only to malignant fibrous histiocytoma [10, 11, 12]. Liposarcomas may be defined as malignant mesenchymal tumours consisting of lipoblasts [11]. They originate in the connective tissue and their name reflects the fact that variable amounts of adipose tissue are found within the tumour [13]. Since sarcomas, in general, are very rare, there is not much literature on the prognostic factors and optimal treatment of liposarcomas [3]. Compared to other malignant tumours in the extremity, it is uncommon [14].

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Liposarcomas occur mainly in adults [15, 16] with its incidence peaking between 40 and 60 years with a slight predominance towards men [11, 13]. It is much more commonly seen in Caucasians than blacks [17].

Although it occurs at any age, and at any site [8], there is a paucity of data in children due to the rarity in this group [18]. In both age groups, the thigh is the most frequent location [13, 14, 18, 19, 20], however they may also arise in the inguinal area and popliteal fossa [13, 14]. Tumours in the popliteal fossa, such as the index case, are likely to be malignant [21]. Other factors suggesting malignancy in the index case was a mass greater than 5 cm and a deep seated mass [7]. Attachments to other structures also suggest malignancy. A mass is commonly the only symptom which may grow intermittently (index case) or progress steadily [5, 20]. In comparison to other soft tissue sarcomas, liposarcomas tend to be large partially because the patient tends not to have other symptoms and they often have a deep location which may not allow the patient to appreciate the mass earlier [5, 13, 20]. Both are possible reasons why the patient's mass grew to be large.

Diagnosis of liposarcoma is now less common because of stricter diagnostic criteria. Tumours such as atypical lipoma, spindle cell lipomas and pleomorphic lipomas were all once previously categorised as liposarcoma [15]]. Early diagnosis and referral to specialist centres are necessary for optimal outcome [5].

Many different typing systems have been described [1, 19, 22, 23]. The most commonly used system is Enzinger and Weiss [19, 24]. The system recognises four variants of liposarcoma: well differentiated, myxoid, round cell and pleomorphic. The importance of the histological subtypes cannot be understated in terms of being a prognostic factor [15, 24, 25, 26]. Well differentiated is the most common subtype [11, 27, 28]. They tend to arise in the limbs or retro- peritoneum in the middle aged or elderly population accounting for greater than 50% of reported cases [3, 11]. This subtype is low grade and often is grossly very large, that is, greater than 20 cm [28]. This was the subtype in the index case. Histologically it is characterised by proliferation of mature appearing adipocytes with variable numbers of atypical hyperchromatic cells either between the adipocytes or within dense fibrous septae [17].

The second most common groups are the myxoid and round cells (30-40% of all liposarcomas) which are seen in a younger population [11, 29]. Asano 2012 reviewed information on 58 patients with myxoid and round cell tumours. The median age at presentation was 46 years old (range; 18-80 years). It is felt that the myxoid and round cells types are a continuum of a single subtype [19, 24, 27, 28]. The higher the proportion of the round cell component is the worse the outcome [19, 27], with higher rates of metastasis [24, 29]. There are two forms of myxoid tumour: The first is a well differentiated liposarcoma subtype which is similar to the well differentiated histological group, and the second form is characterised by distinctive genetic reciprocal translocation of two genes.

De-differentiation of a well differentiated subtype may be due to a clonal evolution in which local foci of other cells are found such as malignant fibrous histocytoma [14, 28]. De-differentiated and pleomorphic subtypes accounts for approximately 5%, occurring in older patients and presenting in the limbs or retroperitoneum [11, 29]. The pleomorphic subtype is most commonly seen in patients in their fourth decade [19]. It has the worst prognosis based on disease free survival rates of 39% at ten years [24, 30], and recurs in a third of cases [24].

The lung is the commonest site of early metastasis [20, 22, 30] in all subtypes except the myxoid subtype which has a strong propensity for extrapulmonary metastasis, for example, spine, retroperitoneum and axilla [30]. Patients with the myxoid subtype require a more careful follow-up including assessment of the thorax, retroperitoneum and abdomen [30]. Dedifferentiation is associated with a 15-30% rate of metastasis and an increase risk of local recurrence and increased death risk [13, 28]. Radical excision is thus required to achieve local control plus or minus adjuvant radiotherapy [28]. The pleomorphic type is also associated with an increased risk of local and distant spread [11, 29]. The overall metastatic potential of liposarcoma therefore varies widely from 20-70% [11, 14, 24]. Comparison between studies is difficult because of small numbers of patients and the wide variety of the subtypes [30].

Histology affects subsequent clinical behaviour where low grade lesions (well differentiated) are associated with high local recurrence rates but have almost no propensity to metastasize. Poorly differentiated or high grade tumours are often clinically aggressive with a high incidence of local recurrence as well as distant metastasis [3, 12, 31]. Although the different subgroups have different clinical courses in terms of clinical features and survival outcome, current clinical practice has not been optimised according to different histological subtypes and clinical protocols [3]. Specific treatment protocols are lacking in the literature for liposarcoma other than treatment with wide resection [17]. Treatment decisions and prognosis are based on a classification system that depends on morphological and genetic features of the tumour [5, 32]. Kim et al [3] looked at defining the distinctive clinical features by assessing prognostic factors in 94 liposarcoma patients. His multivariate analysis demonstrated that histological subtype was an index prognostic factor for survival. Higher grade tumours (de-differentiated, round cell, pleomorphic) were associated with a fivefold increase in

mortality rates compared with the well differentiated subtype. Zagars et al [24] found that the most important factor influencing outcome in terms of local control, metastasis or survival rates was histological subtype. Berlin et al [33] and Lietman et al [17] found a strong association between disease specific survivorships and grade.

Despite there being the same universal guidelines in managing extremity sarcomas, management must be individualised [34]. Management however remains controversial [4]. A multidisciplinary team approach allows for streamlining the complexities and intricacies of treatment and thus providing optimal treatment [4, 34]. Goals include eradicating local disease, control of metastasis and salvaging a functional limb without compromising survival [4, 5]. Prior to the use of radiotherapy, amputation was a standard therapeutic treatment [5, 35].

Radiation has been proven to facilitate local control and when used in combination with limb sparing surgery has decreased the need for amputation [5, 6, 24]. Patients such as the index case with inadequate margins may benefit from adjuvant therapy [6]. In cases where a marginally resectable tumour is present, neoadjuvant therapy may increase the likelihood of a margin negative resection with subsequent preservation of function [34]. The potential wound complications [34] and the potential for radiation induced sarcoma which is typically seen two to three years post treatment [11] dissuaded the patient from opting for radiotherapy.

Grossly positive margins have a significantly worse prognosis compared with negative or microscopic positive margins [36]. Conversely when adequate surgical margins are achieved, local recurrence is unlikely even in high grade tumours, making radiotherapy unnecessary in these cases [33, 37]. The likelihood of local recurrence is partially related to whether the excision is marginal, wide or radical [37]. Although many studies recommended a margin of at least 2cm of gross margins around the tumour, this is usually limited by a normal critical structure [37]. Most liposarcomas in the extremity cannot be excised with a wide margin, but one should aim for at least a marginal resection [13]. Despite positive margins being a risk factor for local recurrence, overall survival is unaffected [5, 37]. This was the rationale for performing a marginal resection in some areas of the tumour in the index case. Leaving close margins near vital structures are acceptable for a limb salvage procedure [5]. Baldini et al [37] in their study of 74 sarcoma patients, 23 of which had liposarcoma, were all treated with excision alone. Six patients had positive margins. None of the six patients had local recurrence. The four patients with recurrence had histological evidence of tumour involvement less than 1cm within the resection margins. He found no relationship between recurrence and tumour grade, stage and depth, on further analysis though the study had limited statistical power. Ribuffo et al [38] in reviewing liposarcoma in the thigh found no correlation between histological grade, surgical treatment and progression of disease. Conversely, Orson et al [31] looked at 211 cases with a mean age of 52.9 years and found a 45% variation in survival rates due to differences in histological grade, Enneking stage and tumour size. Various soft tissue reconstructive procedures have allowed for more aggressive resection leading to a lower likelihood of an intralesional resection [4, 5]. Incompletely excised tumour may be subsequently re-excised inclusive of the prior incision followed by radiation therapy [6, 14, 24]. With the index case refusing radiation therapy, he had been counselled on the need for re-excision once there is future evidence of recurrence. In the index case's favour, is the fact that no patient had demised solely to local disease in Linehan et al [12] study as microscopic margins were not a predictor of local recurrence when managed with adjuvant radiotherapy.

Sarcomas in general often appear grossly to be contained in a well-defined capsule but microscopic disease is often beyond the psuedocapsule, reactive zone, prior biopsy site scar and a cuff normal tissue via a longitudinal incision [5, 34].

Although limb sparing surgery plus or minus radiotherapy have shown good results, the role of chemotherapy remains controversial [14]. Adjuvant chemotherapy is meant to eradicate micrometastasis with the ultimate goal of prolonging time to recurrence and overall survival [17]. Lietman et al [17] performed a thorough literature search and found no randomised prospective studies analysing the effectiveness of various chemotherapy regimes, protocols or indications in the treatment of liposarcoma. Chemotherapy sensitivity varies significantly between liposarcoma subtypes with a higher response rate in the myxoid and round cell subtypes compared with the well differentiated subtype [32]. Eilber et al [39] found that ifosfamide based treatment in liposarcoma patients improved disease free survival states in patients with tumours greater than 10 cm (such as the index case) however there is little data to support use of chemotherapy in low grade liposarcoma because of their low metastatic spread potential [13].

In a 20 year retrospective review of 63 patients with liposarcoma; age, gender and tumour size were not shown to be statistically significant in terms of patient survivorship however, it was felt that the sample size was too small to make a definitive conclusion [17]. Older age was a poor prognostic factor in some studies [23, 33].

Location has been found to be an independent prognostic factor, since liposarcomas in the extremity has a better prognosis than retroperitoneal liposarcoma [12, 17, 23] despite there being a lower percentage of low grade tumours in the extremity [17].

In most soft tissue sarcomas, recurrence occurs within two years. Follow up every three months with clinical and radiological imaging via MRI or ultrasound is recommended to identify local recurrence and chest CT for pulmonary metastasis [5, 37]. If no lesion is identified, review may be six monthly after 2 to 3 years. There is as yet no clinical evidence of local recurrence in the index case. Since the adjuvant radiotherapy has been refused by the patient, he will be monitored clinically and radiologically and if recurrence occurs, re-excision will hopefully treat recurrence in this margin positive patient. Based on the well differentiated subtype, the index case is unlikely to have metastasis or mortality even if recurrence does occur. With improved understanding of patterns of recurrence in extremity liposarcoma, there will be earlier identification of subclinical metastatic disease thus allowing aggressive salvage treatment and improved overall survival [30]. Dalal et al [23] have published subtype specific liposarcoma prognostic nomograms that can efficiently integrate multiple prognostic variables which allow one to predict the probability of recurrence and death. This information is useful in counselling patients and in some cases to reassure [23]. This also allows high risk patients to be identified and undergo intense surveillance and be considered for adjuvant or neoadjuvant therapy [23].

In a very recent study, Knebel et al [40] conducted a retrospective study on 133 patients with a diagnosis of liposarcoma. The median age was 55.1 years (14-86 years). Upon analysing the data he concluded that the histological subtype, tumour size, presence of metastasis, local recurrence post resection and negative resection margins were all independent factors which determined disease specific survival.

IV. Conclusion

The histological subtype and resection margin status have been found to be independently associated with disease specific survival. Adjuvant radiotherapy has been found to have a bigger impact on overall survival rates as well as disease free survival, in low grade sarcomas than high grade ones.

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