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Factors Predictive of Survival in Synovial Sarcoma; a Review of the Literature

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Abstract

Background: Synovial sarcomas are a rare malignant mesenchymal soft tissue tumour, with generally poor prognosis due to a high degree of local invasiveness and propensity to metastasise. Despite sharing a common translocation signature, tumour behaviour is highly variable with wide heterogeneity in patient outcomes. Limited data exists in the literature regarding prognostic factors and treatment modalities. This review aims to summarise current literature findings to help better prognosticate patients and evaluate treatment modalities.

Methods: A critical literature review of the English language literature from 2000 was conducted utilising MEDLINE (via OVID) software and searching the terms "synovial sarcoma" alone or in combination with "prognosis", "radiotherapy", "chemotherapy" and "neoadjuvant therapy". 331 articles were retrieved; full-text articles specifically evaluating outcomes in synovial sarcoma were included; unavailable full texts (68) case reports (113) and non-synovial sarcoma related (73) articles were excluded. Further articles (20) were identified by cross referencing the bibliographies of relevant papers; in total 97 papers remained eligible for analysis.

Conclusion: Adverse prognostic factors include: increasing age at diagnosis, male gender, increasing tumour size, deep sited tumours, monophasic and poorly differentiated subtypes, increasing necrosis, increasing mitotic activity, higher genomic complexity, non-specialist treatment centre and inadequate margins. New immunohistochemical markers are emerging that may also assist with prognostication. Radiotherapy improves local control and may offer further survival benefits. Chemotherapy should be reserved for high risk patient groups.

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Introduction

Synovial sarcomas (SS) are rare malignant mesenchymal soft tissue tumours(STS), accounting for approximately 6-8% of all malignant STS [1,2]. They are considered high grade with poor prognosis, due to a high degree of local invasiveness and propensity to metastasise [1]. It commonly occurs in adolescents and young adults, mostly within the age range of 15-40 years [3]. Contemporary 5-year overall survival (OS) rates for SS have been reported as ranging from 61% to 73% [1,3-6]. Thetranslocation of (X;18)(p11;q11), results in either of three possible gene fusions, SYT-SSX1, SYT-SSX2 or rarely SYT-SSX4 and is highly specific for SS, present in 95% cases. Despite this common translocation, SS interestingly displays various histological subtypes. SS may be characterised by epithelial-like and spindle cell components arranged in either a monophasic pattern, composed entirely of spindle cells; biphasic pattern, composed of both spindle cells and epithelial cells; or poorly differentiated form. SS demonstrate highly diverse clinical and biological behaviours, with substantial heterogeneity in patient outcome. Various prognostic factors and treatment modalities have been described, however due to the rarity of the tumour, high level evidence remains lacking. In recent years, many new studies have emerged proposing various prognostic factors in patients with SS; while some findings are consistent with previously published findings, others remain contentious. The purpose of this review is to summarise recent literature findings to facilitate better prognostication of patients, which may then help inform treatment choices.

Predicting Survival Outcome

Gender

The effect of gender on survival outcome has been variably reported. Some early studies found that gender had nosignificant effect on overall survival [7-9]. A number of more recent studies

have reported male gender to have inferior survival outcomes on significant on univariate analysis [10-13]. These studies have all been limited by relatively small sample sizes (*n=42*-165) and lack of multivariate analysis concordance. Most recently, a large analysis of the Surveillance, Epidemiology and End Results (SEER) database from North America found that male gender on multivariate analysis conferred an adverse survival outcome, with a hazard ratio (HR) compared to female gender for OS of 1.63 (P<0.001, *n=1189*) [6].Validation of the SEER findings are needed from other large population studies before male gender can be completely described as an adverse prognosticator. Despite this gender effect seems likely, given that to date all studies that have reported gender to have significant survivorship influence haveimplicated male gender with worse outcomes. It has been speculated that differences in survival by gender may relate to male sex having a higher incidence of SYT-SSX1 fusion which has been associated with worse survival [14].

Age at diagnosis

Presenting age at diagnosis is a very important determinant of survival outcome. Most studies have found age at diagnosis to be significantly correlated with survival outcome on univariate analysis, with younger patients having improved survival compared to those of older age [1,3,5,6,11,15-25]. This has also been demonstrated by various large studies on multivariate analysis [5,6,16,18,19]. The effect of age on survival outcome is striking. Sultan et al in a large analysis from the SEER database reported that the 5-year cancer specific survival was 83% for children/adolescents compared to 62% for adults (P<0.001, *n=1268*) [18]. This finding has been recently corroborated by another large analysis from the Netherlands Cancer Registry [19]. Vlenterie et al. [18], recently reportedsignificantly different (P<0.001, *n=461*) survivals of various age groups with localised SS at diagnosis; children had the best 5-year OS outcome (89.3%), followed by adolescents and young adults (73%), adults (54.7%) and elderly (43%). The effect of age was maintained on their multivariate analysis, with adults having a HR of 4.10 relative to children (P<0.001, *n=613*) [19]. Age at diagnosis therefore appears to be an important prognosticator in SS.

Tumour size

Of all the prognostic factors evaluated in this review, tumour size was found to be the prognostic factor most consistently predictive of OS, event free survival (EFS) and metastases free survival on univariate analysis(MFS) [3,4,6,11,14,16,20,22,26-41]. Although increasing tumour size likely reflects underlying disease aggression, tumour size is also likely to be confounded in part by other variables such as tumour location and delayed time to presentation. Despite this, a number of large studies have conducted extensive multivariate analysis and found tumour size to be an independent prognostic factor when adjusted for various variables [6,14,19,20,28,33,41]. The effect to which tumour size affects survival has been variably reported. Generally, it appears that larger tumour size, especially ≥5cm predicts poor outcome, whilst size <5cm is linked to more favourable outcome. Canter et al. [14] reported that tumours 5-10cm conferred a HR of 2.75 relative to ≤5cm (P=0.01, *n=255*). Similarly, Palmerini et al. [23], found tumours >5cm to confer a RR of 2.20 compared to ≤5cm (P=0.002, *n=250*) [41]. In the large study by Naing et al. larger tumour size conferred a HR of 1.13 (P < 0.001, *n=1189*); however the threshold and relationship between size and HR was unclear [6]. To date it appears tumour size may reliably be used in prognostic stratifications, and while the precise relationship between size and outcome is unclear, tumour size ≥5cm is likely to represent a poorer prognosis.

Tumour depth

Depth of tumour has also been shown to be predictive of outcome, with superficial SS conferring better prognosis than deep on univariate analyses [31]. In the study by Stanelle et al. [28], superficial SS were associated with significantly better 5-year OS; 90% compared to 68% deep (P = 0.03, *n=111*) [28]. Yaser et al. [1], also reported a survival benefit with superficial tumours, with a 5-year OS of 86% for superficial tumours compared to 45% deep tumours (P=0.012, *n*=51) [1]. Both of these studies have been limited by small study numbers and univariate analyses. A more recent study by Vlenteri et al. [19], in a larger cohort (*n=461)* also found tumour depth to be an important factor on univariate analysis, however this lost significance on multivariate analysis [19]. The effect of tumour depth on survival may beconfounded by difficulty in achieving adequate surgical margins and possible delays in diagnosis, and further robust validationon multivariate analyses are needed to adjust for these variables.

Tumour site

Various studies have investigated the impact of SS tumour site on survival. Location has been demonstrated to be important, with axial sites conferring the worst prognosis [16], and distal extremity sites conferring more favourable outcomes [34]. A small study by Paulino et al. [17] noted that extremity sites had better local control rates than non-extremity sites, with non-extremity sites treated with wide local excision conferring a HR of death of 10.14 times the HR of extremity sites treated with wide local excision (P=0.001, *n=44)* [17]. A more modest finding by Orbach et al in contrast found on multivariate analysis that non-limb site conferred a HR of 2.5 compared to limb location (P=0.04, *n=88*) [39]. Ferrari et al. [41], in a pooled study of STS, of which 107 patients had SS, found that head-neck sites versus extremity sites conferred a HR of 2.0 (P = 0.001, *n=301*) [16], Naing et al. [6], also found similar results with head-neck sites conferring a HR of 1.88 (P = <0.001, *n=1189*) and thoracic sites conferring a HR of 2.66 (P = <0.001, *n=1189*) [6]. This relationship between site and outcome has been corroborated by most studies, and non-extremity tumour location has demonstrably worse survival outcomes [1,6,11,15-17,19,28,30,39,42].

Tumour stage/grouping

Tumour stage unsurprisingly has also been found to be predictive of OS, with higher stage at diagnosis linked to worse OS [8,13,20,39]. Naing et al. [6], found that regional staging compared to localised staging conferred a HR of 1.61 (P <0.001, *n=1189*) [6]. Okcu et al. [43], found that Intergroup Rhabdomyo sarcoma Study Group (IRS) group III and IV had particularly poor prognosis; IRS group III had a HR of 2.7 of whilst IRS group IV conferred a HR of 14.1 [43]. An early study by Trassard et al also found on multivariate analysis that higher American Joint Committee on Cancer (AJCC) stage was associated with less favourable prognosis [13]. A problem with staging tools is that different institutions utilise different tools; from the previous examples, Naing et al. [6], utilised a SEER staging tool, Okcu et al. [43,44], utilised the IRS grouping method and Trassard et al assigned AJCC stages [13]. It seems likely that higher stage, regardless of grouping tool utilised, is associated with inferior outcome, however more consistent use of grouping tools by varying institutions would help to evaluate this prognostic tool further and enable easier comparison of results.

Histologic subtype

Conflicting results regarding the effect of histological subtype on survival outcome have been published. In this review, a number of studies found that monophasic histology conferred adverse survival outcome compared to biphasic histology [1,17,45,46], with one study by Koh et al. [30], even finding that monophasic subtype was the single most important prognostic factor after metastasis at presentation, with a HR of 5.714 (P=0.00247, *n=41*) [30]. Not all studies have been concordant; Okcu et al. [43] noted a non-significant trend of patients with biphasic histology having reduced progression free survival compared to monophasic histology (P=0.14, *n=42*) [44]. Furthermore, an earlier study by Hasegawa et al found that poorly differentiated SS conferred a HR of 1.94 compared to monophasic or biphasic histology subtype (P=0.0095, *n=44*) [4], a similar finding was later found by De Silva et al in their analysis of the Scottish Bone Tumour Registry, with the presence of poorly differentiated areas conferring a HR of 8 on multivariate analysis relative to no poorly differentiated areas (P=0.004, *n=51*).These studies have mostly been limited by relatively small sample sizes and heterogenous study groups. A recent large analysis of the National Cancer Data Base of the American College of Surgeons revealed new observations, with biphasic histology demonstrated a better 5-year survivorship (65%) compared to monophasic SS (56%) (P<0.031, *n=3756*) [45]. Poorly differentiated SS was found to the worst prognosis compared to other histology subtypes, with a 5-year survivorship of 52% (P<0.001, *n=3756*) [45]. From these results, it therefore seems probable that monophasic, and in particularly, poorly differentiated SS subtypes confer a worse prognosis than the biphasic subtype.

Tumour necrosis

A number of studies have reported that the presence of spontaneous tumour necrosis in SS affects survival outcome [4,11,42,46-48]. Increasing tumour necrosis especially confers worse outcome; this was demonstrated in a recent study by Setsu et al. which found varying 5-year OS rates for no necrosis (81.9%), ≤50% necrosis (35.9%) and >50% necrosis (37%) (P<0.0001, *n=112*) [11]. De Silva et al. [46], also found that higher percentage tumour necrosis resulted in an increased likelihood of metastases on multivariate analysis, with a HR of 5.06 conferred (P=0.016, *n=51*) [46]. Although these studies are of modest sizes, increased tumour necrosis may reflect increasing underlying tumour aggression and may assist prognostication.

Mitotic activity and genomic complexity

Increasing mitotic activity has been implicated as conferring worse outcome in a number of studies [22,38,49]. Although a component of the FNCLCC grading system, mitotic activity has recently been demonstrated to be an independent prognostic factor on multivariate analyses by Song et al (mitoses ≥10 per high powered field HR 9.182 (P=0.004, *n=103*) and Tarkan et al. [49]. (mitoses ≥10 per high powered DFS HR 0.3; P=0.017, *n=96*). Chakiba et al. [50], recently found that genomic complexity is significantly associated with MFS, with higher genomic index complexity conferring a HR of 3.79 (P=0.02, *n=65*) [50]. Gene expression profiling by Przybyl et al. [51], in a small group (*n*=54) has demonstrated that AURKA and KIF18A are significantly upregulated in SS patients that develop metastasis/local recurrence or present with metachronous metastatic disease, compared to patients that do not develop local recurrence or metastasis [51]. Further work is needed in this area, however it appears differences in biological behaviour and clinical outcome may be attributed to significant differences in genomic composition.

Tumour grade

SS has conventionally been considered a high-grade sarcoma [9]. Notwithstanding, SS may be graded according to the published criteria of Fedération Nationale des Centres de Lutte le Cancer (FNCLCC) as either Grade II or Grade III[52]. Mounting evidence supports utilising this approach, with a number of studies finding that Grade III confers a worse prognosis than Grade II SS [4,5,9,21,40,42,53]. Indeed, Guillou et al. [9], found that histologic grade III was the most significant prognostic factor for both disease specific survival (RR 3.77; P<0.0001, *n=130*) and metastases free survival (RR 3.56; P<0.0001, *n*=130) on multivariate analysis [9]. Despite this, until further research is forthcoming it is best to consider SS as high grade until the prognostic importance of grading in SS is resolved [54].

Immunohistochemical markers

A number of other immunohistochemical markers have been explored. Palmerini et al recently found on multivariate analysis that nuclear expression of CXCR4 (negative expression 5-year OS HR 0.3; P=0.003, *n*=88) and IGF-1R (negative expression 5-year OS HR 0.4; P=0.04, *n=88*) are independent adverse prognostic factors for patient survival [23]. Other antibodies suggested to be of prognostic value include secernin-1[55], FGFR3[56], surviving [57], EZH2 [58], dysadherin [59] and HER-2 [60]. This area is clearly evolving and further work is needed, but such research may offer unique prognostication tools and development of targeted therapies.

Surgical setting

Multiple studies have found on review that unplanned biopsy and surgical treatment at centres other than tertiary cancer care centres result in worse oncological outcomes and increased risk of mismanagement and worsened prognosis [4,53,61,62]. An early study by Choong et al. [7], found a significantly higher rate of local recurrence (LR) in patients with SS treated outside their own institution, with 11 of 13 patients who developed LR treated by definitive surgery outside of their own institution (P<0.0001, *n*=113) [7]. A later study by Ipach et al. [29], found that patients treated with STS at external centres had twice the rate of local recurrence (LR) compared to their own specialist cancer centre institution (45.7% at 5 years *v* 21.2%; P = 0.013, *n=118*) [29]. This was further corroborated by Yaser et al. [1], who also found reduced local recurrence free survival (LRFS) for externally treated patients; with 5-year LRFS rates of 80% *v* 21% (P=0.001, *n=51*); 5-year OS was also significantly adversely affected (0% *v* 78%; P=0.003, *n=51*) [1]. Difference in survival outcomes and local recurrence rates likely reflect better planned surgery and multidisciplinary care and highlight the importance for treatment at specialist centres where possible.

Surgical margins

Several studies have found that surgical margins are an important prognostic factor, with inadequate margins conferring higher risk of LR and metastases compared to clear wide margins [5,6,11,21,27,35,40,63]. Control of margin status is also important in improving survival outcomes. A reasonably large study by Italiano et al. found margin status on multivariate analysis to be significant for both OS and LRFS, with uncertain margins conferring a HR for OS of 2.43 (P=0.005, *n*=237) and a HR for LRFS of 2.43 (P=0.027, *n*=237) [5]. More recent studies by Yaser et al. [1] and Stanelle et al. [28], have also found similar findings. Yaser et al. [1], found a significant difference (P = 0.001, *n=51*) in 5-year local recurrence free survival (LRFS) between negative margins (92%) and positive

margins (45%) and 5-year OS (86.5% *v* 50.3%, P = 0.009) [1]. Stanelle et al. [28], also found that margin status significantly correlated with LR (but not metastasis), with negative margins having a LR rate of 16.3% compared to 47.6% in patients who had positive margins (P = 0.002, *n=111*) [28]. Recently, Tarkan et. [49] alfurther demonstrated in their cohort that achieving adequate margins significantly affected both 5-year OS (74% *v 28%*; P=0.003, *n=69*) and 3-year disease free survival (47% *v* 21%; P=0.005, *n=69*) [49]. Despite this, some studies have also found that clear margins did not affect event free survival or OS [32,64]. For instance, Brecht et al. [33] found that margin status did not significantly affect OS (P=0.36, *n*=150) or LRFS (P=0.42, *n=150*) [65]. It seems probable that surgical margins significantly affect the likelihood of LR, however further studies are required to elucidate to what extent margins must be obtained to offer survival benefit, particularly in the setting of attempted limb salvage where patients may be more acceptable of higher level of LR rates if the risk is low.

Chemotherapy

SS is regarded as a relatively chemo-sensitive subset of STS, and a recent assessment of use in extremity sarcomas in the United States found that patients with SS were more likely (OR 1.48; P<0.001, *n=8649*) to receive post-operative chemotherapy than other extremity sarcomas [66]. Despite this, the role of neoadjuvant chemotherapy in SS is controversial. Some studies have found improved OS and metastases free survival [21,36,61,67], whilst others have found it does not affect OS or metastases rate [8,26,68]. Regimes are typically ifosfamide based and use appears to be more established in paediatric patients with SS. An early study by Ferrari et al. [67], in a cohort of 271 mixed adult and paediatric patients with SS found that among patients treated with surgery, the 5-year MFS was 60% for those treated with chemotherapy compared to 48% for those who were not [67]. This benefit of chemotherapy appeared to be greatest for patients age > 17 years who had tumours measuring > 5 cm (MFS, 47% [chemotherapy] vs. 27% [no chemotherapy]. The conclusions by Ferrari et al. [67], were however limited in that they reported raw data findings (*n=271*) only and did not attempt any univariate or multivariate analysis; and may further be confounded by selection bias as benefit was greatest for patients at higher risk [67]. Eilber et al. [36], later evaluated the use of ifosfamide chemotherapy for high risk (median tumour size 7cm, monophasic histology 70%) adult patients with SS. They demonstrated an independently improved (HR 0.4; P=0.03, *n=101)* distant-recurrence free survival (DRFS) compared to patients who did not receive chemotherapy. A later study by Chen et al. [36] in a cohort of 76 patients also found thatchemotherapy benefited patients with stage IIB/III SS in disease specific survival (73% with chemotherapy *v* 31% with no chemotherapy, P = 0.001), 5-year MFS (62% with chemotherapy *v* 19% with no chemotherapy, P = 0.008) and a prolonged time to metastases (25 months with chemotherapy *v* 9 months with no chemotherapy, P = 0.001) [21]. A later multi-institutional study by Ferrari et al. [67] demonstrated good response to neoadjuvant ifosfamide-doxorubicin chemotherapy with 3-year event free survival rates of 91.2% and 74.4% for intermediate and high risk groups respectively, compared to 91.7% for low risk patients who received surgery alone [69]. Other groups have published opposing findings. Italiano et al found that neither neoadjuvant or adjuvant chemotherapy had significant impact on OS, LRFS or DRFS (P>0.05, *n=237*) [5]. Stanelle et al.[28], in a retrospective review of 111 patients with SS finding that chemotherapy (using doxorubicin, a combination of doxorubicin and ifosfamide, or a combination of ifosfamide and etoposide) did not correlate with improved 5-year survival in any patient group (however the authors do note that the lack of chemotherapy-associated benefit may represent a selection bias for patients who were administered chemotherapy) [28]. An additional study by Al-Hussaini et al. [26], in a mixed study of adult and paediatric patients also found similar 5-year event free survival outcomes between patients who received chemotherapy to those who did not (62.6% *v* 71.5%; P=0.48, *n=102*), with no statistical difference in outcome [26]. Some of these discrepancies may be accounted for by different chemotherapy regime protocols and different patient selection criteria; studies with positive findings have mostly selected high risk patients. Currently insufficient evidence exists to support the routine use of chemotherapy in SS, and use is better restricted for higher risk patient populations. Further study, particularly in adult populations is required to elucidate which patients should receive adjuvant chemotherapy.

Radiotherapy

For localised disease, surgical resection is frequently combined with radiotherapy. This was shown by Sherman et al in a large retrospective study (*n=1242*) where in addition to surgical resection; 7% patients with SS were treated with neoadjuvant radiotherapy, 25% with post-operative radiotherapy and 22% with both radiotherapy and chemotherapy [66][66].Many studies have evaluated the role of radiotherapy. Most have found that routine use of radiotherapy results in betteroutcome, especially demonstrated by improved local control rates [1, 6, 16, 29, 31, 68]. Cumulative doses >60 Gy have been demonstrated in STS to have the best impact on local control (P=0.003, *n*=155) and OS(P=0.048, *n*=155) compared to ≤60 Gyin one study by Laskar et al.[31]. Interestingly, Ipach et al. found that the risk of death doubled if no adjuvant chemotherapy or radiotherapy was provided, although the effect of chemotherapy from radiotherapy was unclear[29]. A study by Italiano *et al.* found that while radiotherapy did not improve DRFS or OS, it significantly improved LRFS, with a HR of 0.43 in favour of use (P=0.026*, n=237*) [5]. Comparable results were found by Palmerini et al, who found a RR of 1.86 for LRFS when radiotherapy was omitted (P=0.02, *n*=250) [41]. Similarly, Song et al found the use of radiotherapy to confer a LRFS benefit, with a HR of 0.195 in favour of use (P=0.0028, *n=103*); a benefit in progression-free survival was also demonstrated with a HR of 0.248 (P=0.006,*n=103*)[38].Most recently, Naing et al.evaluatedthe use of radiotherapy in SS in their large SEER database[6]. They found that radiotherapy provided significant improvement to OS (HR = 0.65; P=0.005, *n=1189*) and disease specific survival (HR = 0.62; P=0.003, *n=1189*); with a benefit maintained at 5-years[6]. These and other studies provide strong evidence for the use of RT in the treatment of localised SS, due toboth improved local control rates and potential OS benefit.

Conclusion

Despite their rarity, emerging research is assisting in the development of improved prognostic tools for patients and clinicians. This has been assisted by multi-institutional collaboration and data from large national registries. Although sharing a common fusion translocation, synovial sarcomas are a heterogenous subset of soft tissue sarcomas. Adverse prognostic factors include increasing age at diagnosis, male gender, increasing tumour size, deep sited tumours, monophasic and poorly differentiated subtypes, increasing necrosis, increasing mitotic activity, higher genomic complexity, non-specialist treatment centre and inadequate margins. New immunohistochemical

markers are emerging that may also assist with prognostication. Surgical resection with wide margins provides the mainstay of treatment; radiotherapy improves local control and may offer further survival benefits. Chemotherapy should be reserved for high risk patient groups until further research emerges.It is imperative that sarcoma centres collaborate to form multi-institutional randomised trials to raise the quality of evidence available to improve patient outcomes.

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