



## Understanding radiotherapy and its potential for use in novel combination trials

### Soft tissue sarcoma

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#### UK incidence

<1% of all cancers.

#### Introduction

Soft tissue sarcomas are rare tumours arising from connective tissue. The variation in anatomic site, histological diagnosis and biology make these cancers complex to manage. Most occur in the extremities (60%), but tumours can also arise in the retroperitoneum (20%), abdominal/thoracic wall (15%) and head and neck (5%) (1). For those patients that develop metastatic disease, this usually occurs with lung metastases secondary due to haematogenous spread within 2 years of the initial primary presentation (2). Risk factors are recurrent disease, high/intermediate grade, deep-seated tumours, central tumours and large tumours (>5 cm). 5-year survival for all stages is 50–60% (3).

**Surgery:** The primary curative treatment is surgery, aiming to achieve resection margins of 1–2 cm while maintaining function where possible. Where margins are likely to be close, surgery combined with radiotherapy (RT) allows equivalent local control rates while maintaining function (4–6).

**Radiotherapy:** Sarcomas are considered to be relatively radioresistant tumours. The indications for using RT include high/intermediate grade, large tumours and close or potentially close tumour excision margins. Treatment is delivered either post-operatively or pre-operatively depending on the clinical circumstances. Pre-operative radiotherapy allows a smaller volume to be treated to a lower dose (50 Gy in 25 fractions) as the tumour mass can be defined, but with a higher risk of post-operative complications (7). Patients treated with pre-operative radiotherapy, compared to those treated with post-operative radiotherapy, were found to have less long term fibrosis, joint stiffness and oedema, all of which can affect limb function (8). Certain types of sarcoma may be more radiosensitive and be more amenable to pre-operative RT, such as myxoid liposarcomas (9). Post-operative radiotherapy is given to the whole of the tumour bed, covering the surgical scar to a dose of between 60–66 Gy in 30 to 33 fractions. This is delivered using conformal radiotherapy or IMRT. The VORTEX study is a randomized controlled trial investigating the use of smaller margins in the post-operative setting in any patient with an extremity soft tissue sarcoma who may require post-

operative radiotherapy; it is currently recruiting within the UK. Retroperitoneal sarcomas are difficult to treat with RT either pre- or post operatively (10). There are critical organs at risk within the abdomen which have a lower radiotolerance than the doses needed to control soft tissue sarcoma. There is no role for concurrent chemoradiotherapy at present. High dose palliative radiotherapy can be given over a shorter time.

**Chemotherapy:** Sarcomas are also considered to be relatively resistant to chemotherapy. There is no established role for neoadjuvant/adjuvant chemotherapy in standard clinical care outside of a clinical trial. Chemotherapy is frequently given for metastatic disease and first line agents include doxorubicin and ifosfamide, which have highest response rates of approximately 20% (11). There is no standard second line treatment.

### Soft tissue sarcoma biology

There are around 50 different histological types. The most common are: pleomorphic sarcomas (30%), liposarcomas (15%), leiomyosarcomas (12%) and synovial sarcomas (10%). Sarcomas are broadly divided into two groups: those which have defined genetic translocations and those with complex karyotypes (12). Most soft tissue sarcomas have no specific genotypes. Chromosomal translocations resulting in fusion proteins can be identified using fluorescence *in situ* hybridisation (FISH) and comparative genomic hybridisation (CGH) such as Ewing's sarcoma (EWS-FL1), clear cell sarcoma (EWS-ATF1), myxoid liposarcoma (TLS-CHOP) and synovial sarcoma (SSX-SYT), amongst others. Mutations and deletions of tumour suppressor genes *TP53* and the retinoblastoma gene have been found in 30–60% of soft tissue sarcomas. Oncogenes implicated include N-myc, MDM2, c-erbB2 and the ras family (13).

Gastrointestinal stromal tumours (GIST) account for approximately 5% of soft tissue sarcomas. Like other sarcomas, primary treatment is surgical and they are chemoresistant (14). They are characterised by the overexpression of c-KIT, a tyrosine kinase (TK) receptor. Development of a TK inhibitor, imatinib, has led to significant improvement in the survival of patients with GIST (15-16).

### Therapeutic opportunities with radiotherapy in soft tissue sarcoma

Since the primary modality of treatment is surgery, histological specimens can be used to collect predictive and prognostic information. Patients having pre-operative RT can be assessed before and after RT. Studies would enable oncologists to determine which patients benefit from RT and which do not. This may allow for the prediction of late tissue toxicity, leading to dose escalation for those with higher tolerance.

#### Phase I and II trials

- For patients receiving pre- or post-operative RT there is an opportunity to improve local control by combining novel agents with RT.
- Functional imaging and blood biomarker studies are required to investigate whether such biomarkers can predict treatment response.

- Image-guided RT has the potential to improve localisation and reduce margins leading to normal tissue sparing and the possibility of dose-escalation. Using advances in RT such as intensity-modulated RT, and different techniques such as a simultaneous integrated boost, could be used to deliver different doses to different parts of the tumour.

### **Phase III trials and registration strategy**

Soft tissue sarcomas occur in a heterogeneous patient population with multiple sub-groups that may show different responses to treatment. National/international collaborative studies are required to recruit sufficient numbers.

### **Opportunities for early phase trials with novel agents and radiotherapy**

1. Some soft tissue sarcomas arise from the endothelium (e.g. angiosarcomas). Anti-angiogenic drugs not only target the tumour blood supply, but may also have a direct anti-tumour effect (17).
2. Preclinical studies have shown an effect of matrix-metalloproteinase inhibitors in reducing invasion and metastases (18). Reduction of matrix-metalloproteinase expression may also reduce acute and late radiotherapy toxicity (19).
3. Agents inhibiting the growth receptor pathway (1, 13) resulting in increased radiosensitisation:
  - a. EGFR and HER2 targeted therapies
  - b. TK inhibitors
  - c. AKT (PI3-kinase)/mTOR inhibitors
4. Agents targeting cell cycle and apoptosis pathways, given the high rate of *TP53* mutations in soft tissue sarcoma (20).

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