MULTIDISCIPLINARY DIAGNOSIS AND THERAPY OF SOFT TISSUE SARCOMAS

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Soft tissue sarcomas (STS) are a heterogeneous group of tumours

- STS are **challenging to diagnose and treat** due to their rarity, various clinical presentations, disease course and multiple subtypes
- ≥ 100 different histological subtypes of sarcoma of soft tissues are known

Sarcoma is often initially misrecognised and misdiagnosed

- Therefore, sarcoma is often **not treated according to clinical practice guidelines**

Specialist centres

- Referral to a specialist centre is **key to ensure correct diagnosis and treatment** by multidisciplinary experts resulting in improved outcomes
- However, **many patients with primary STS are still treated in nonreferral centres** by unplanned resection of the tumour and then later referred to specialist centres

‘Whoops’ procedures

- **Inadequate diagnostic procedures and treatment**, e.g. enucleation of the tumour as initial surgery without initial imaging or biopsy, are observed in a large fraction of patients

STS, soft tissue sarcoma
MULTIDISCIPLINARY APPROACH AND REFERRAL TO SPECIALIST CENTRES IS KEY

- Refer the following tumours to a reference centre for biopsy, diagnosis and treatment:
  - Superficial tumours > 5 cm in diameter
  - All deeply located tumours (below the muscle fascia)

ESMO-EURACAN, European Society for Medical Oncology-European Reference Network for rare adult solid cancers; STSs, soft tissue sarcomas
The management of soft tissue sarcoma (STS) requires an organized, structured approach involving many disciplines

- If an MDT is not utilized, a large proportion of patients with STS may be subject to an initial suboptimal surgery resulting in the need for more extensive surgery and radiation than the original tumor may dictate.

- **Diagnosis** of the primary lesion, distal metastasis, or subsequent local recurrence requires the use of advanced imaging (MRI +/- contrast, or CT for biopsy) as well as the expertise of appropriately trained pathologists.

- Surgeries, especially for wide re-excision after unplanned primary excision of soft tissue sarcoma, often require plastic surgeons for optimal tissue coverage.

**IMPORTANCE OF MULTIDISCIPLINARY TEAM (MDT)**

CT, computed tomography; MDT, multi-disciplinary team; MRI, magnetic resonance imaging; STS, soft tissue sarcoma

STANDARD DIAGNOSTIC PROCEDURES

**Imaging**

MRI is the preferred imaging modality\(^1\)–\(^3\)
- MRI is considered to have superior contrast resolution and a better ability to demonstrate subtle changes in soft tissues\(^1\)
- CT and ultrasound have limited roles in diagnosis of STS\(^1\)

**Biopsy**

Biopsy is the gold standard for diagnosis\(^1\)
- The standard approach is multiple core needle biopsies (needles >16 G)\(^3\)
- Excisional biopsy is an option in selected cases\(^3\)
- Fine-needle aspiration is not recommended outside of centres that have specific expertise in the procedure\(^3\)

**Grading/staging**

Histological type:\(^4\)
- World Health Organization (WHO) classification
- Grading:\(^2\) NCI/FNCLCC grading systems
- Staging:\(^5\) AJCC/UICC staging system

AJCC, American Joint Committee on Cancer; CT, computed tomography; FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; MRI, magnetic resonance imaging; NCI, National Cancer Institute; STS, soft tissue sarcoma; UICC, International Union Against Cancer; WHO, world health organisation

MRI IMAGES OF STS WITH INTERNAL HETEROGENEITY

STS, soft tissue sarcoma
Patient scans provided by Rutkowski P, personal communication 2019
IMPORTANCE OF DIAGNOSTIC BIOPSY IN SOFT TISSUE SARCOMA

SARCOMA – CORE NEEDLE BIOPSY NOT OFTEN PERFORMED!

90 mm!

BREAST TUMOUR – CORE NEEDLE BIOPSY ALWAYS PERFORMED!

7 mm!

Patient scans provided by Rutkowski P, personal communication 2019
Primary tumour – resection of entire tumour with a margin of normal tissue around the pseudocapsule plane is desirable to prevent local recurrence.

Lymph node metastases are generally rare in soft tissue sarcoma (approx. 3% of cases)
- The sarcomas that most frequently metastasize to lymph nodes in adults are:
  - Angiosarcoma
  - Epithelioid sarcoma
  - Clear cell sarcoma

The most common site of distant metastases is the lung (from the extremities)
- Metastases may also occur infrequently in the skin, soft tissues and liver

STS, soft tissue sarcoma
**(1) RT can be omitted in selected cases; optional: isolated limb perfusion in highly selected cases.**

**(2) RT can be omitted in selected deep cases and added in selected superficial cases; to be administered preoperatively if problematic postoperatively.**

**(3) Extremity and superficial trunk, G3, deep, >5 cm**

ChT, chemotherapy; MDT, multidisciplinary team; R0, no tumour at the margin; R1, microscopic tumour at the margin; RT, radiotherapy; STS, soft tissue sarcoma

LRFS ACCORDING TO TUMOUR STATUS AT TREATMENT START IN REFERENCE CENTER

<table>
<thead>
<tr>
<th>Tumour status at beginning of therapy in tertiary centre</th>
<th>5-year LRFS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumour</td>
<td>86.1%</td>
<td>78.5-94.5%</td>
</tr>
<tr>
<td>Clinical recurrence</td>
<td>52.1%</td>
<td>36.6-74.3%</td>
</tr>
<tr>
<td>Scar after nonradical surgery</td>
<td>73.3%</td>
<td>53.6-100.0%</td>
</tr>
</tbody>
</table>

CI, confidence interval; LRFS, local relapse-free survival
LRFS ACCORDING TO SURGICAL MARGINS

Margins positivity

<table>
<thead>
<tr>
<th>Radical surgery margins status</th>
<th>5-year LRFS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>77.5%</td>
<td>68.7-87.4%</td>
</tr>
<tr>
<td>R1</td>
<td>60.9%</td>
<td>44.8-82.6%</td>
</tr>
</tbody>
</table>

• Primary planned microscopically radical (R0) resection and multidisciplinary care in a tertiary referral center is crucial in the management of soft tissue sarcomas and has the best prognosis in terms of local control.

CI, confidence interval; LRFS, local relapse-free survival
CAUSE-SPECIFIC MORTALITY BY MICROSCOPIC MARGIN STATUS

10-year mortality
Primary cases

<table>
<thead>
<tr>
<th>Margin Status</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive margin</td>
<td>0.31</td>
<td>0.20-0.42</td>
</tr>
<tr>
<td>Negative margin</td>
<td>0.24</td>
<td>0.20-0.28</td>
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</tbody>
</table>

10-year mortality
Recurrent cases

<table>
<thead>
<tr>
<th>Margin Status</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive margin</td>
<td>0.47</td>
<td>0.34-0.59</td>
</tr>
<tr>
<td>Negative margin</td>
<td>0.34</td>
<td>0.26-0.41</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio
Unplanned excisions of high-grade STS resulted in increased rates of local recurrence but not disease-specific survival.

- **Unplanned excision and tumour bed re-excision**
  - 5-year LRFS: 63.7%
  - 95% CI: 50.7-75.1%

- **Primary planned excision**
  - 5-year LRFS: 89.7%
  - 95% CI: 83.1-94.0%

- **P-value**: P<0.0001

CI, confidence interval; LRFS, local relapse-free survival; STS, soft tissue sarcoma
Certain tissues in the limbs act as natural barriers to tumour spread and separate tissues into distinct anatomical compartments.
Surgeries, especially for wide re-excison after unplanned primary excision of soft tissue sarcoma, often require plastic surgeons for optimal tissue coverage.
NETSARC: A NETWORK OF 26 REFERENCE CENTRES IN FRANCE

- NETSARC is a network of 26 reference sarcoma centers with specialized MDT), funded by INCa

INCa, French national cancer institute; MDTB, multidisciplinary tumour boards; NCI, national cancer institute
QUALITY OF INITIAL SURGERY, INCIDENT PATIENTS

STS AND VISCERAL SARCOMAS OPERATED

R0, resection for cure or complete remission; R1, microscopic residual tumour; R2, macroscopic residual tumour

STS, soft tissue sarcoma
IMPACT OF SURGERY IN REFERENCE CENTRE ON RELAPSE AND SURVIVAL

A NATIONWIDE STUDY OF FSG GETO/NETSARC

• From Jan 2010 to Dec 2014:-
  - 9646 non-metastatic pts aged ≥15, with a first diagnosis of STS/visceral sarcoma
  - 3514 (36%) pts operated in one of the 26 NETSARC reference centres
  - 6132 (64%) pts operated on outside the NETSARC reference centres

• Better observation of the guidelines with pts operated on in NETSARC centres compared to non-reference centres
  - Adequate imaging of the tumour before treatment/surgery (84.7% vs 57.8%, p<0.0001)
  - Biopsy prior to first resection (77.9% vs 32.5%, p<0.0001)
  - MDTB before surgery (56.2% vs 10.4%, p<0.0001)

MDTB, multidisciplinary tumour board; LRFS, local relapse-free survival; OS, overall survival; RFS, relapse free survival; STS, soft tissue sarcoma
Blay J-Y, et al. ESMO 2017 Abstract #14740
Surgical resection at NetSARC reference centres significantly prolonged median LRFS (60 vs 41 months, p< 0.001) and RFS (25 vs 21 months, P<0.001) compared to surgery at another centre.

Surgery in reference centre was an independent good prognostic factor using a Cox model for LRFS (HR 0.60), RFS (HR 0.79) and OS (HR 0.68), p<0.001 for all.

LRFS AND RFS BETTER IN NETSARC CENTRE

LRFS, local relapse-free survival; OS, overall survival; RFS, relapse free survival
Blay J-Y, et al. ESMO 2017 Abstract #14740
### MANAGEMENT OF SARCOMA PATIENTS IN REFERENCE CENTRES IMPROVES OUTCOMES

#### MULTIVARIATE ANALYSIS FOR LRFS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>1.761</td>
<td>0.000</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1.330</td>
<td>0.000</td>
</tr>
<tr>
<td>Size</td>
<td>1.002</td>
<td>0.000</td>
</tr>
<tr>
<td>Surgery in NetSARC center</td>
<td>0.669</td>
<td>0.000</td>
</tr>
<tr>
<td>Gender</td>
<td>0.878</td>
<td>0.01</td>
</tr>
<tr>
<td>Depth</td>
<td>0.881</td>
<td>0.07</td>
</tr>
</tbody>
</table>

HR, hazard ratio; LRFS, local relapse-free survival
Blay J-Y, et al. ESMO 2017 Abstract #14740
SURGERY IN REFERENCE CENTRES IMPROVES SURVIVAL OF SARCOMA PATIENTS

NATIONAL NETSARC REGISTRY

R0, resection for cure or complete remission; R1, microscopic residual tumour; R2, macroscopic residual tumour; R unk, unknown surgery

SUMMARY

- Sarcomas are very rare tumours with non-specific characteristics and are often mistaken for other soft tissue masses such as lipoma or other benign tumours.
- Proper diagnosis and referral to specialist centres is important.
- For the following tumours, it is important to diagnose the soft tissue mass prior to removal by surgery using a core needle biopsy:
  - Superficial tumours > 5 cm in diameter
  - All deeply located tumours (below the muscle fascia)
- Following biopsy:
  - If tumour is benign it can be removed by surgery
  - If sarcoma is suspected or diagnosed, refer to a specialist centre for multimodal treatment (surgery, radiotherapy and chemotherapy)
- Referral to specialist centres with access to multidisciplinary teams (diagnostic and treatment teams) is essential for improved outcomes.
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