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# MULTIDISCIPLINARY DIAGNOSIS AND THERAPY OF SOFT TISSUE SARCOMAS

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# DISCLAIMER

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# BACKGROUND

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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

1. Rutkowski, P et al. Clin Orthop Relat Res 2013;471:860-70. 2. Fletcher CDM, et al. (eds). WHO Classification of Tumours of Soft Tissue and Bone 2013. 3. Blay J-Y, et al. Ann Oncol 2019;30:1143-53

# ESMO-EURACAN GUIDELINES

## MULTIDISCIPLINARY APPROACH AND REFERRAL TO SPECIALIST CENTRES IS KEY

Soft tissue and visceral sarcomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up

P. G. Casali, N. Abecassis, H. T. Aro, S. Bauer, R. Biagini, S. Bielack, S. Bonvalot, I. Boukovinas, J. V. M. G. Bovee, T. Brodowicz, J. M. Broto, A. Buonadonna, E. De Álava, A. P. Dei Tos, X. G. Del Muro, P. Dileo, M. Eriksson, A. Fedenko, V. Ferraresi, A. Ferrari, S. Ferrari, A. M. Frezza, S. Gasperoni, H. Gelderblom, T. Gil, G. Grignani, A. Gronchi, R. L. Haas, B. Hassan, P. Hohenberger, R. Issels, H. Joensuu, R. L. Jones, I. Judson, P. Jutte, S. Kaal, B. Kasper, K. Kopeckova, D. A. Krákorová, A. Le Cesne, I. Lugowska, O. Merimsky, M. Montemurro, M. A. Pantaleo, R. Piana, P. Picci, S. Piperno-Neumann, A. L. Pousa, P. Reichardt, M. H. Robinson, P. Rutkowski, A. A. Safwat, P. Schöffski, S. Sleijfer, S. Stacchiotti, K. Sundby Hall, M. Unk, F. Van Coevorden, W.T.A. van der Graaf, J. Whelan, E. Wardelmann, O. Zaikova & J. Y. Blay, on behalf of the ESMO Guidelines Committee and EURACAN

STSs are ubiquitous in their site of origin and are often managed with multimodality treatment. A multidisciplinary approach is, therefore, mandatory in all cases, involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists and paediatric oncologists, as well as nuclear medicine specialists and organ-based specialists, as applicable. Management should be carried out in reference centres for sarcomas and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually. These centres are involved in ongoing clinical trials, in which the enrolment of sarcoma patients is common. This centralised referral should be pursued as early as at the time of the clinical diagnosis of a suspected sarcoma. In practice, referral of all patients with a lesion likely to be a sarcoma would be recommended. This would mean referring all patients with an unexplained deep mass of soft tissues, or with a superficial lesion of soft tissues having a diameter of > 5 cm. Quality criteria are needed for sarcoma reference centres and, increasingly, reference networks.

- 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

Cascali, PG et al. Ann Oncology 2018;29:iv51-iv67.

# IMPORTANCE OF MULTIDISCIPLINARY TEAM (MDT)

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- **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

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

Siegel GW, et al. J Multidiscip Health 2015;8:109-15

# STANDARD DIAGNOSTIC PROCEDURES

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## 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

1. Ilaslan H, et al. Cleve Clin J Med 2010;77 Suppl 1:S2; 2. Grimer R, et al. Sarcoma 2010;2010:506182;
3. Casali P & Blay JY. Ann Oncol 2010;21:198; 4. Fletcher C, et al. Pathology and Genetics of Tumours of Soft Tissue and Bone. World Health Organization Classification of Tumours. 2012; 5. Edge S, et al. AJCC Cancer Staging Manual. 7th edn. 2009.

# MRI IMAGES OF STS WITH INTERNAL HETEROGENEITY

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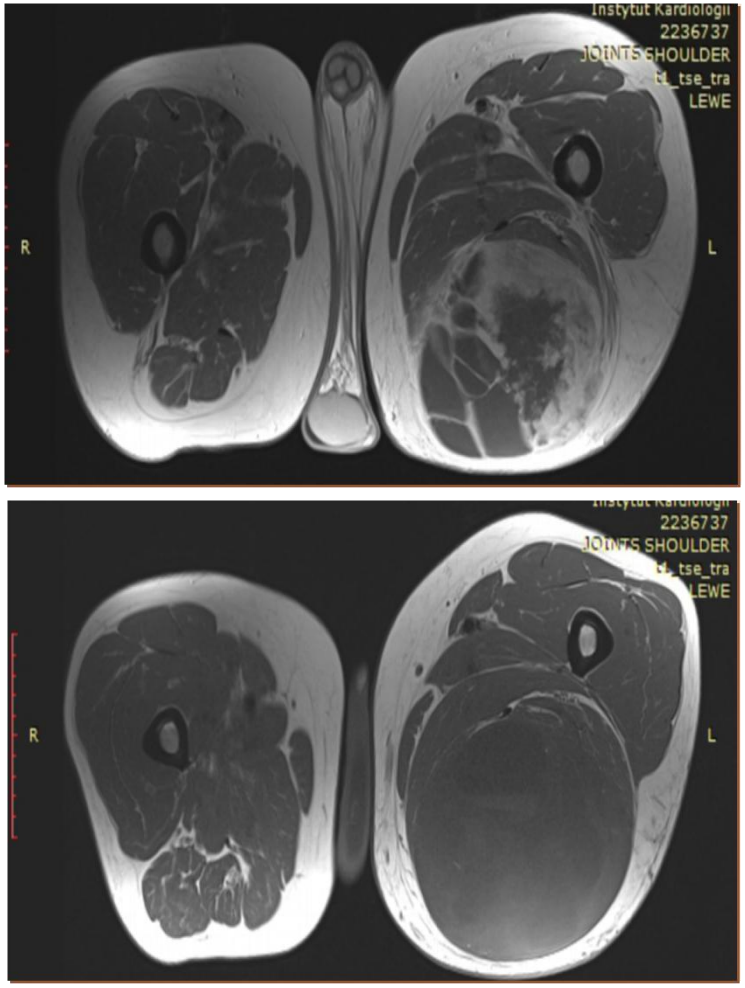


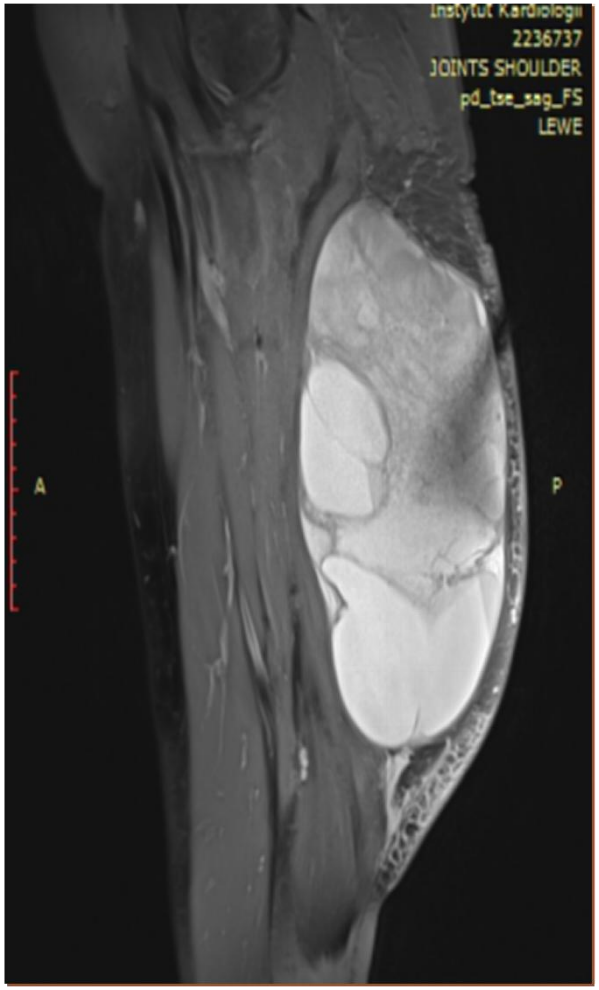


STS, soft tissue sarcoma

Patient scans provided by Rutkowski P, personal communication 2019

# IMPORTANCE OF DIAGNOSTIC BIOPSY IN SOFT TISSUE SARCOMA

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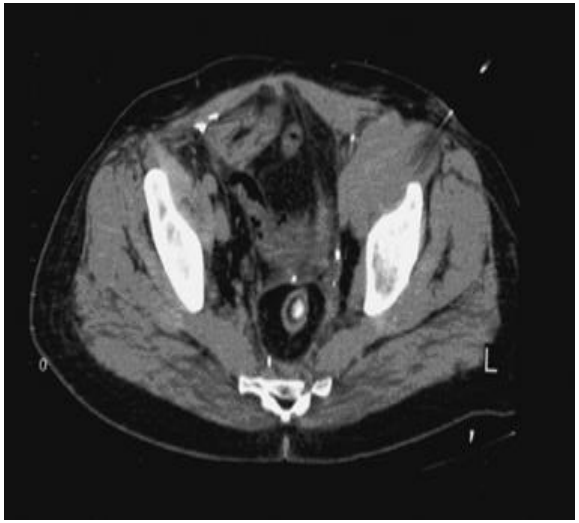
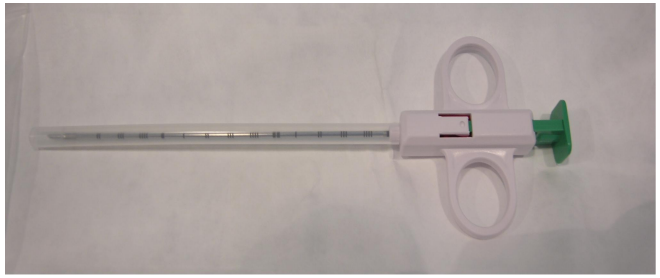
## SARCOMA – CORE NEEDLE BIOPSY NOT OFTEN PERFORMED!

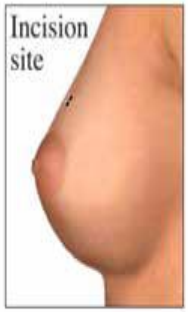
90 mm!

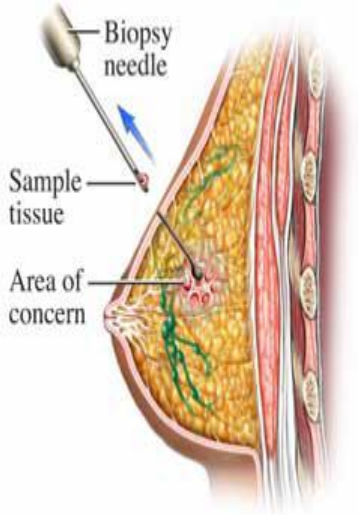




## BREAST TUMOUR – CORE NEEDLE BIOPSY ALWAYS PERFORMED!

7 mm!




Patient scans provided by Rutkowski P, personal communication 2019

# STS PATHOLOGY

- **Primary tumour** – resection of entire tumour with a margin of normal tissue around the psuedocapsule 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

Keung EZ, et al. Eur J Surg Oncol 2018:44(1):170-177

# MANAGEMENT OF LOCALISED, CLINICALLY RESECTABLE SOFT TISSUE SARCOMA

## ESMO EURACAN GUIDELINES

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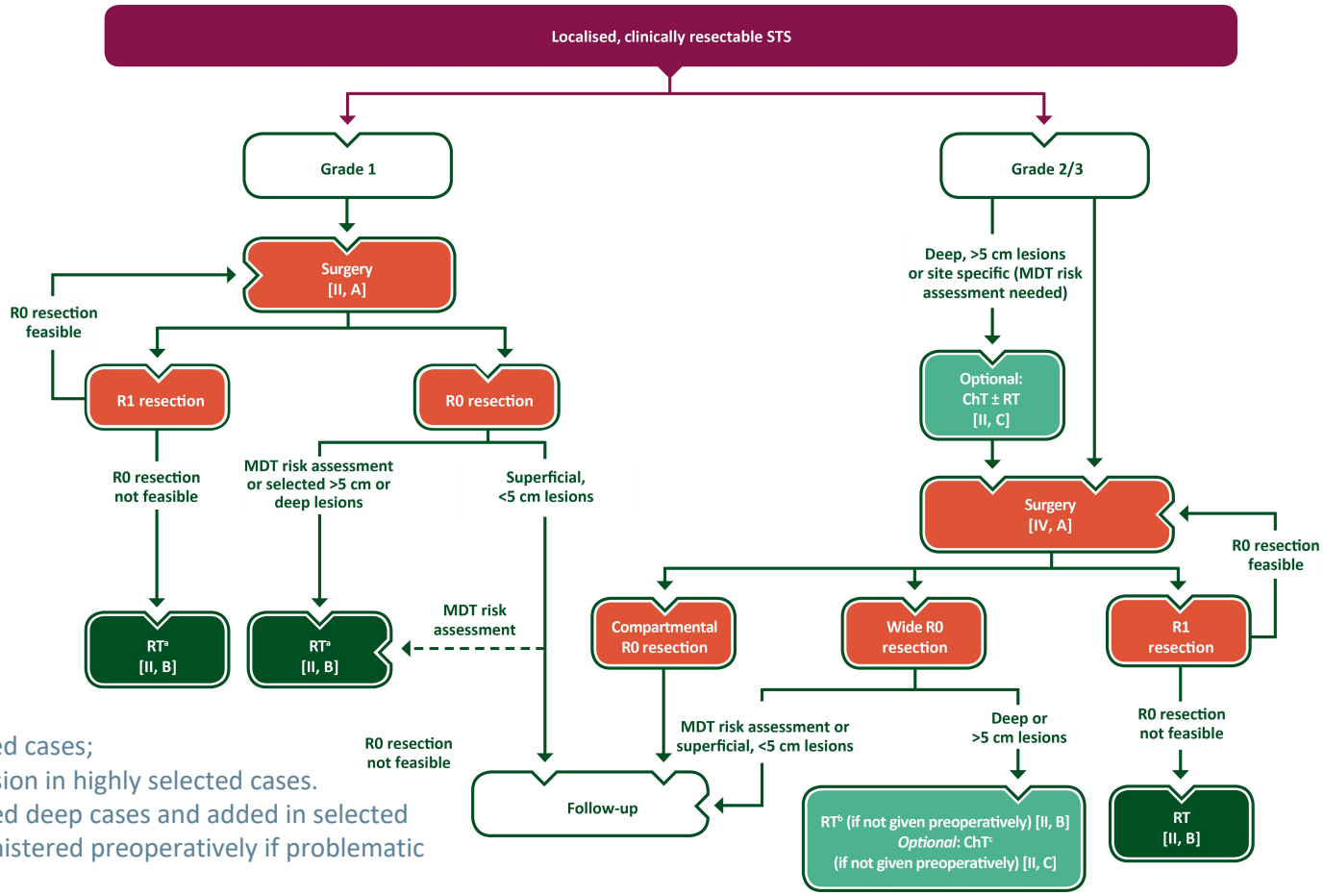
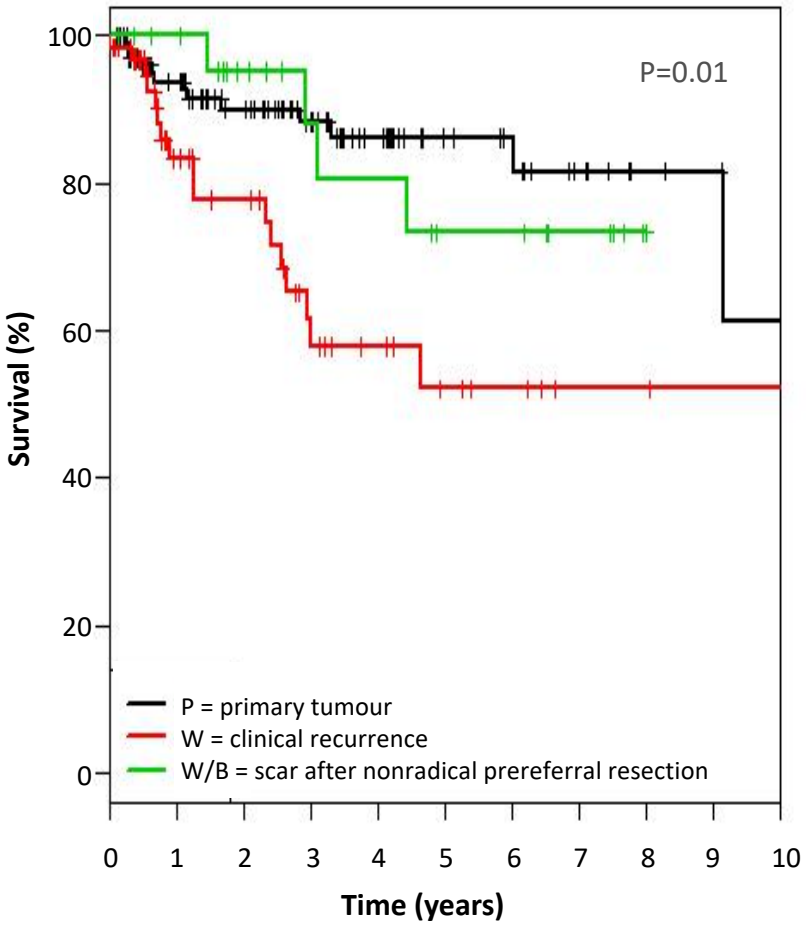



[a] RT can be omitted in selected cases;
optional: isolated limb perfusion in highly selected cases.
[b] RT can be omitted in selected deep cases and added in selected superficial cases; to be administered preoperatively if problematic postoperatively
[c] Extremity and superficial trunk, G3, deep, >5 cm

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

Cascali PG, et al. Ann Oncol 2018;29:iv51-iv67.

# LRFS ACCORDING TO TUMOUR STATUS AT TREATMENT START IN REFERENCE CENTER

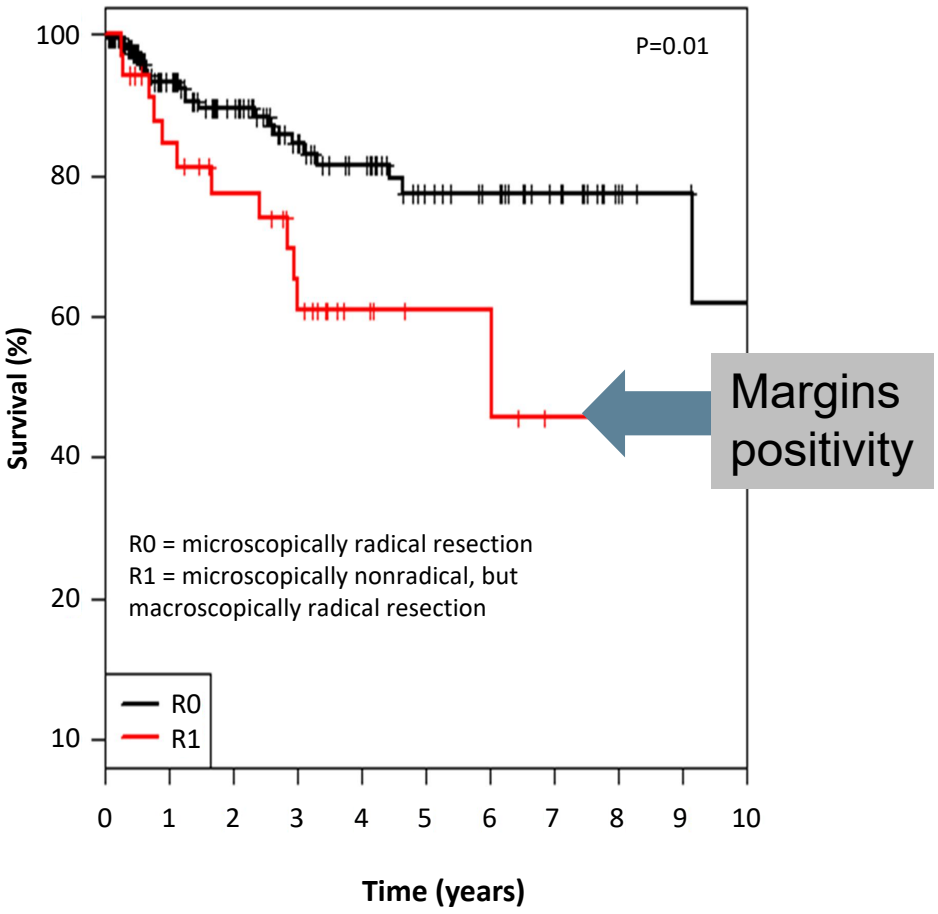



| Tumour status at beginning of therapy in tertiary centre | 5-year LRFS | 95% CI |
|---|---|---|
| **Primary tumour** | 86.1% | 78.5-94.5% |
| **Clinical recurrence** | 52.1% | 36.6-74.3% |
| **Scar after nonradical surgery** | 73.3% | 53.6-100.0% |

CI, confidence interval; LRFS, local relapse-free survival

Rutkowski P, et al. Clin Orthop Relat Res 2013; 471:860-70

# LRFS ACCORDING TO SURGICAL MARGINS




| Radical surgery margins status | 5-year LRFS | 95% CI |
|---|---|---|
| **R0** | 77.5% | 68.7-87.4% |
| **R1** | 60.9% | 44.8-82.6% |

- 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

Rutkowski P, et al. Clin Orthop Relat Res 2013; 471:860-70; Jeys L, et al. CTOS 2010, abstract #902349

# CAUSE-SPECIFIC MORTALITY BY MICROSCOPIC MARGIN STATUS

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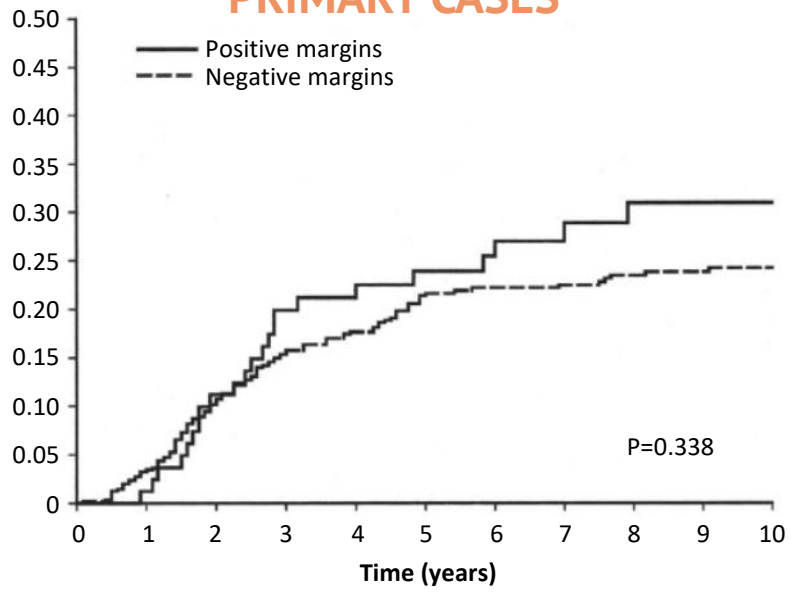
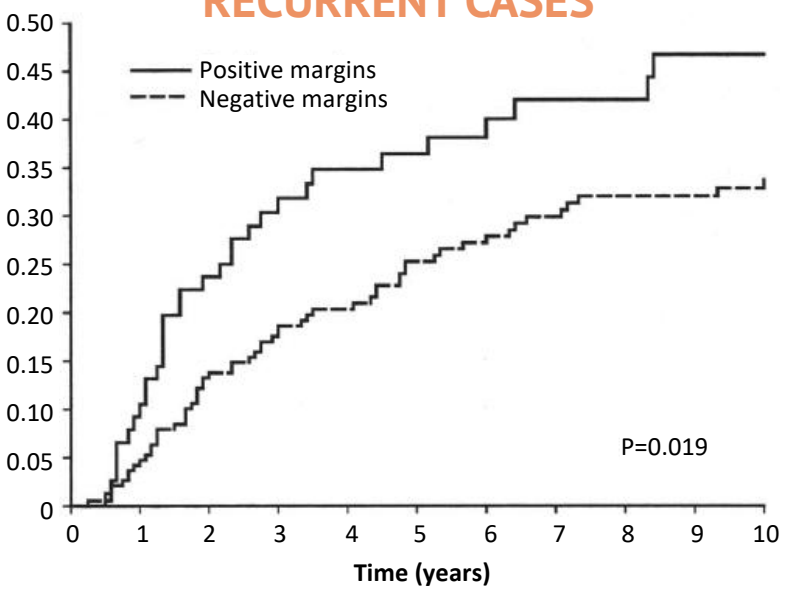
## PRIMARY CASES




## RECURRENT CASES



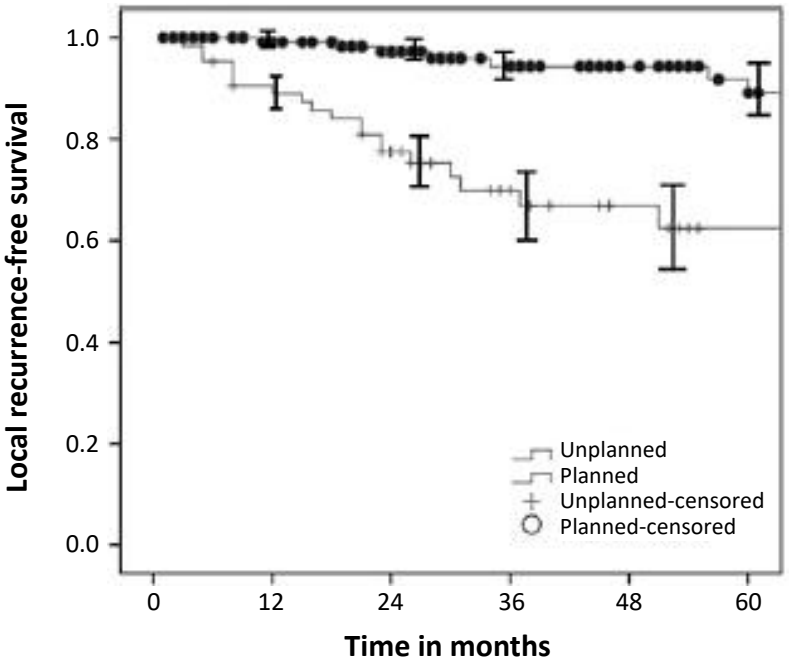

| 10-year mortality Primary cases | HR | 95% CI |
|---|---|---|
| **Positive margin** | 0.31 | 0.20-0.42 |
| **Negative margin** | 0.24 | 0.20-0.28 |

| 10-year mortality Recurrent cases | HR | 95% CI |
|---|---|---|
| **Positive margin** | 0.47 | 0.34-0.59 |
| **Negative margin** | 0.34 | 0.26-0.41 |

CI, confidence interval; HR, hazard ratio

Gronchi A, et al. J Clin Oncol 2005;23:96-104

# UNPLANNED EXCISION OF HIGH-GRADE SOFT TISSUE SARCOMAS




| | 5-year LRFS | 95% CI |
|---|---|---|
| **Unplanned excision and tumour bed re-excision** | 63.7% | 50.7-75.1% |
| **Primary planned excision** | 89.7% | 83.1-94.0% |
| **P-value** | P<0.0001 | |

- Unplanned excisions of high-grade STS resulted in increased rates of local recurrence but not disease-specific survival

CI, confidence interval; LRFS, local relapse-free survival; STS, soft tissue sarcoma

Potter B, et al. Clin Orthop Relat Res 2008;466:3093-100

# NATURAL BARRIERS FOR SARCOMAS

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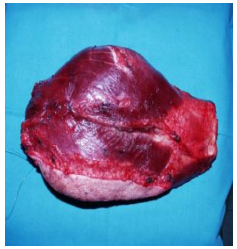
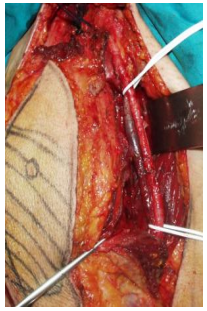
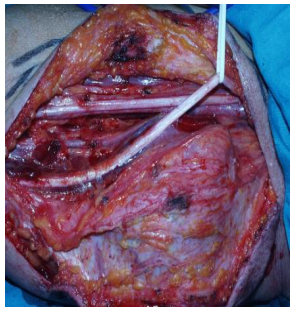
- Certain tissues in the limbs act as **natural barriers to tumour spread** and separate tissues into distinct anatomical compartments



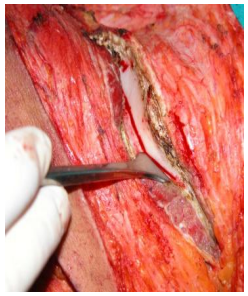
**Muscle fascia**



**Adventitia over vessels**



**Epineurium**



**Periostium over bone**

# WIDE EXCISION OF PRIMARY SARCOMA OF LOWER EXTREMITY

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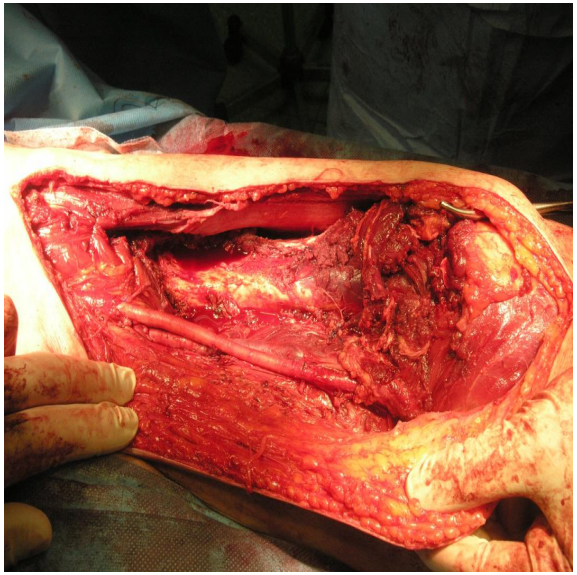
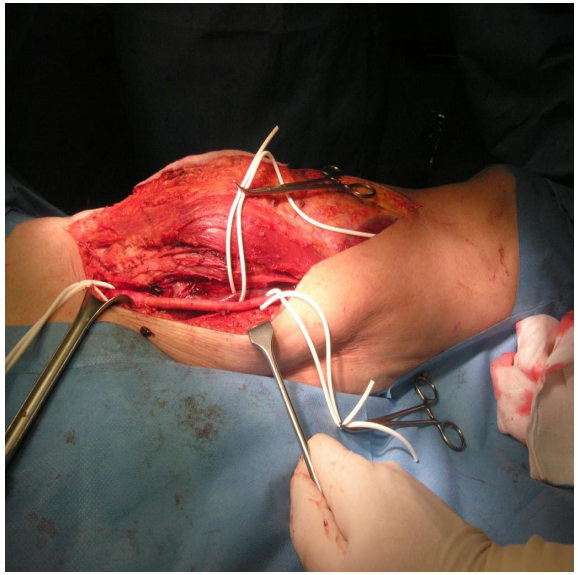
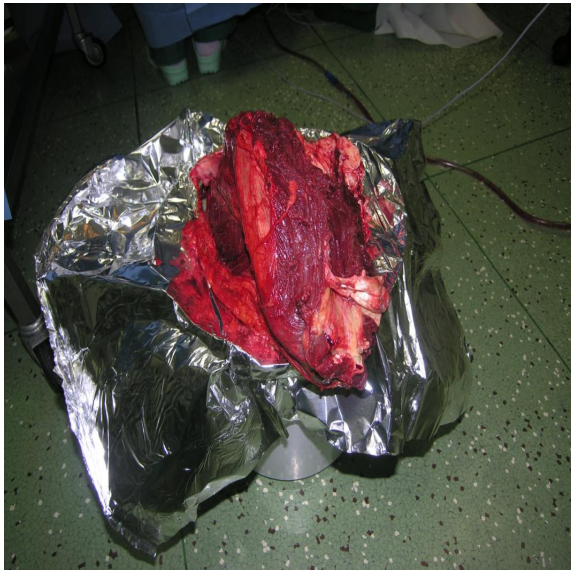
- Surgeries, especially for wide re-excision after unplanned primary excision of soft tissue sarcoma, often **require plastic surgeons for optimal tissue coverage**







# NETSARC: A NETWORK OF 26 REFERENCE CENTRES IN FRANCE

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## Soft tissue

Figure 1a

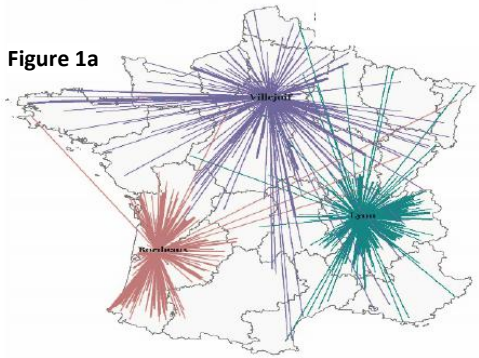
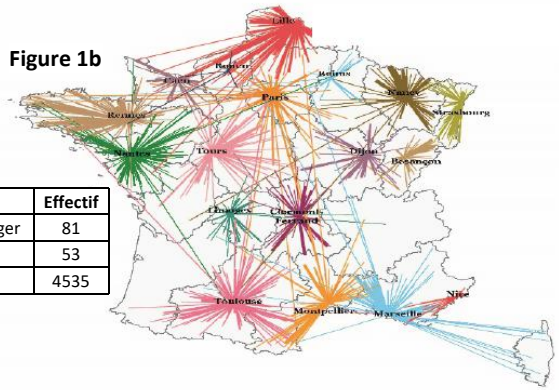


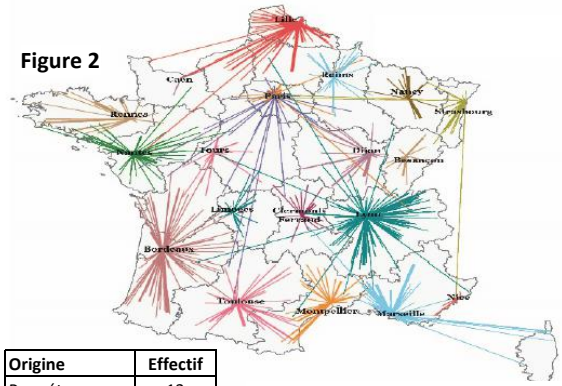
Figure 1b



| Origine | Effectif |
|---|---|
| Pays étranger | 81 |
| DOM-TOM | 53 |
| Total | 4535 |

## Visceral

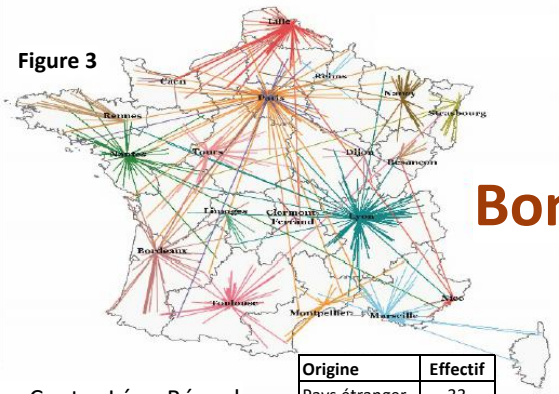
Figure 2



| Origine | Effectif |
|---|---|
| Pays étranger | 12 |
| DOM-TOM | 18 |
| Total | 1326 |

## Bone

Figure 3



| Origine | Effectif |
|---|---|
| Pays étranger | 33 |
| DOM-TOM | 23 |
| Total | 1058 |

Auteur: Yohan Fayel, geographe, Centre Léon Bérard
Source: Base de donnees Netsarc-ResOs (2014)

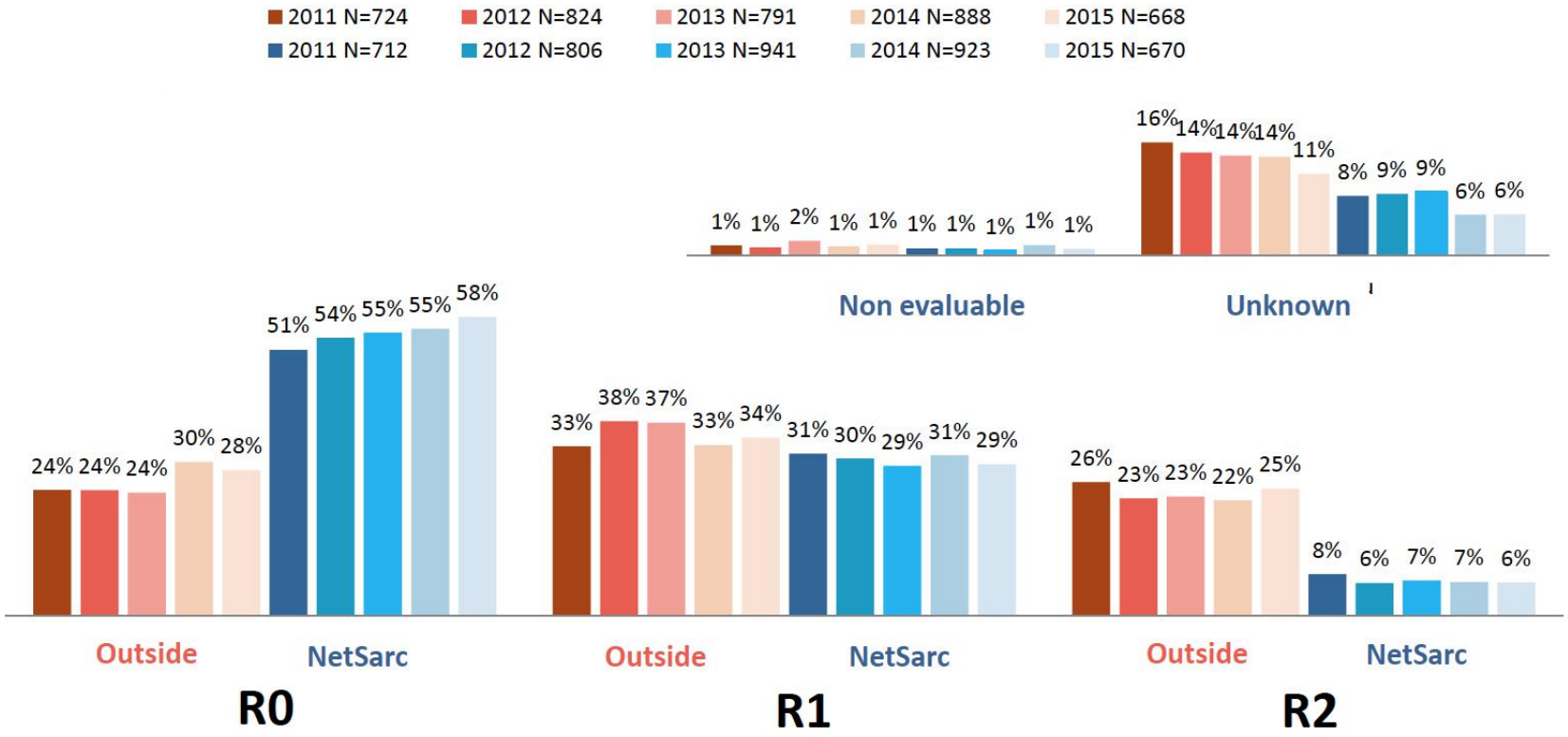
- NETSARC is a network of 26 reference sarcoma centers with specialized MDT), funded by INCa

INCa, French national cancer institute; MDTB, multidisciplinary tumour boards; NCI, national cancer institute

Blay J, et al. presentation at CDDF 2018 (https://cddf.org/files/2018/03/03-JY-Blay.pdf). Accessed 19 November 2019

# 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

Blay J, et al. presentation at CDDF 2018 (https://cddf.org/files/2018/03/03-JY-Blay.pdf). Accessed 19 November 2019

# IMPACT OF SURGERY IN REFERENCE CENTRE ON RELAPSE AND SURVIVAL

## A NATIONWIDE STUDY OF FSG GETO/NETSARC

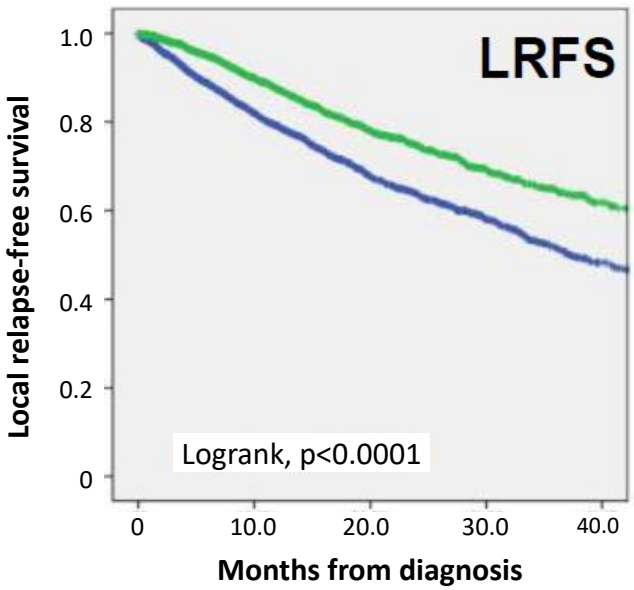
- From Jan 2010 to Dec 2014:-
  - **9646 non-metastatic pts** aged ≥15, with a first diagnosis of STS/visceral sarcoma
  - 3514 (36%) pts operated in one of the 26 NETSARC reference centres
  - 6132 (64%) pts operated on outside the NETSARC reference centres
- Better observation of the guidelines with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

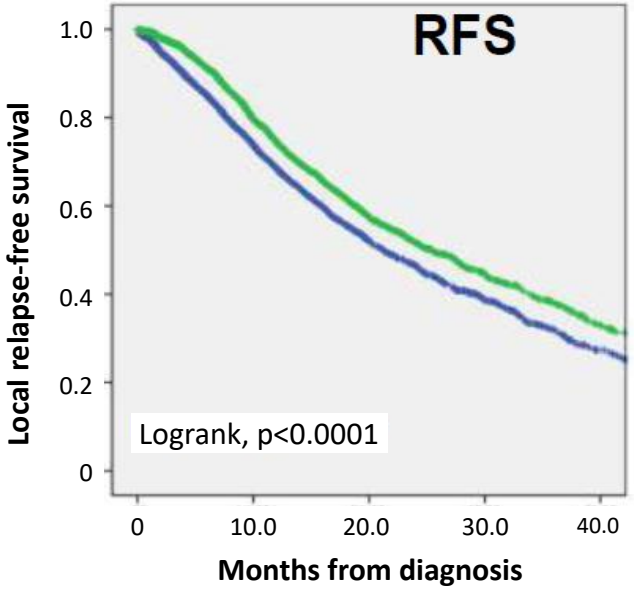
MDTB, multidisciplinary tumour board; LRFS, local relapse-free survival; OS, overall survival; RFS, relapse free survival; STS, soft tissue sarcoma

Blay J-Y, et al. ESMO 2017 Abstract #14740

# LRFS AND RFS BETTER IN NETSARC CENTRE

- 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




Median follow up 30 months

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

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## MULTIVARIATE ANALYSIS FOR LRFS

| Parameter | HR | P value |
|---|---|---|
| Grade 3 | 1.761 | 0.000 |
| Grade 2 | 1.330 | 0.000 |
| Size | 1.002 | 0.000 |
| Surgery in NetSARC center | 0.669 | 0.000 |
| Gender | 0.878 | 0.01 |
| Depth | 0.881 | 0.07 |

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

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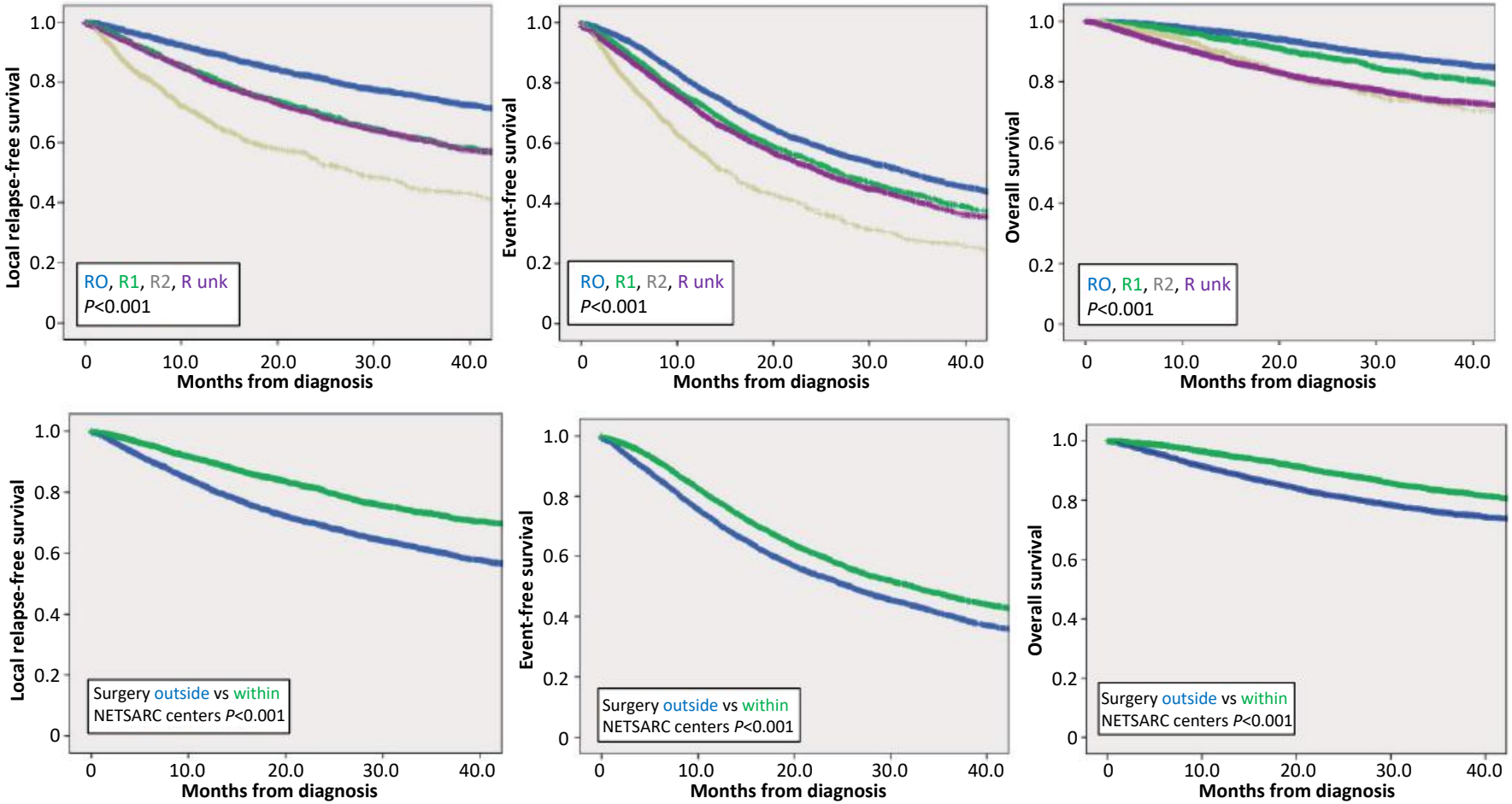
## NATIONAL NETSARC REGISTRY




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

Blay J-Y, et al. Ann Oncol 2019;30:1143-53.

# 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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