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ESMO POCKET GUIDELINES

SARCOMA & GIST

2021

ESMO POCKET GUIDELINES

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ESMO CLINICAL PRACTICE GUIDELINES

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

Gronchi A, Miah, AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, Biagini R, Bielack S, Blay JY, Bolle S, Bonvalot S, Boukovinas I, Bovee JVMG, Boye K, Brennan B, Brodowicz T, Buonadonna A, de Álava E, del Muro XG, Dufresne A, Erikisson M, Fagioli F, Fedenko A, Ferraresi V, Ferrari A, Frezza AM, Gasperoni S, Gelderblom H, Gouin F, Grignani G, Haas R, Hassan AB, Hecker-Nolting S, Hindi N, Hohenberger P, Joensuu H, Jones RL, Jungels C, Jutte P, Kager L, Kasper B, Kawai A, Kopeckova K, Krákorová DA, Le Cesne A, Le Grange F, Legius E, Leithner A, López Pousa A, Martin-Broto J, Merimsky O, Messiou C, Mir O, Montemurro M, Morland B, Morosi C, Palmerini E, Pantaleo MA, Piana R, Piperno-Neumann S, Reichardt P, Rutkowski P, Safwat AA, Sangalli C, Sbaraglia M, Scheipl S, Schöffski P, Sleijfer S, Strauss D, Strauss S, Sundby Hall K, Trama A, Unk M, van de Sande MAJ, van der Graaf WTA, van Houdt WJ, Frebourg T, Casali PG & Stacchiotti S, on behalf of the ESMO Guidelines Committee, EURACAN, and GENTURIS

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Bone sarcomas: ESMO–EURACAN–GENTURIS–ERN PaedCan Clinical Practice Guidelines for diagnosis, treatment and follow-up

Strauss SJ, Frezza AM, Abecassis N, Bajpai J, Bauer S, Biagini R, Bielack S, Blay JY, Bolle S, Bonvalot S, Boukovinas I, Bovee JVMG, Boye K, Brennan B, Brodowicz T, Buonadonna A, de Álava E, Dei Tos AP, Garcia del Muro X, Dufresne A, Erikisson M, Fagioli F, Fedenko A, Ferraresi V, Ferrari A, Gaspar N, Gasperoni S, Gelderblom H, Gouin F, Grignani G, Gronchi A, Haas R, Hassan AB, Hecker-Nolting S, Hindi N, Hohenberger P, Joensuu H, Jones RL, Jungels C, Jutte P, Kager L, Kasper B, Kawai A, Kopeckova K, Krákorová DA, Le Cesne A, Le Grange F, Legius E, Leithner A, López Pousa A, Martin-Broto J, Merimsky O, Messiou C, Miah AB, Mir O, Montemurro M, Morland B, Morosi C, Palmerini E, Pantaleo MA, Piana R, Piperno-Neumann S, Reichardt P, Rutkowski P, Safwat AA, Sangalli C, Sbaraglia M, Scheipl S, Schöffski P, Sleijfer S, Strauss D, Sundby Hall K, Trama A, Unk M, van de Sande MAJ, van der Graaf WTA, van Houdt WJ, Frebourg T, Ladenstein R, Casali PG & Stacchiotti S, on behalf of the ESMO Guidelines Committee, EURACAN, GENTURIS and ERN PaedCan

Ann Oncol 2021;32:1520-36

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Gastrointestinal stromal tumours: ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up

Casali PG, Blay JY, Abecassis N, Bajpai J, Bauer S, Biagini R, Bielack S, Bonvalot S, Boukovinas I, Bovee JVMG, Boye K, Brodowicz T, Buonadonna A, de Álava E, Dei Tos AP, del Muro XG, Dufresne A, Erikisson M, Fedenko A, Ferraresi V, Ferrari A, Frezza AM, Gasperoni S, Gelderblom H, Gouin F, Grignani G, Haas R, Hassan AB, Hindi N, Hohenberger P, Joensuu H, Jones RL, Jungels C, Jutte P, Kasper B, Kawai A, Kopeckova K, Krákorová DA, Le Cesne A, Le Grange F, Legius E, Leithner A, López Pousa A, Martin-Broto J, Merimsky O, Messiou C, Miah AB, Mir O, Montemurro M, Morosi C, Palmerini E, Pantaleo MA, Piana R, Piperno-Neumann S, Reichardt P, Rutkowski P, Safwat AA, Sangalli C, Sbaraglia M, Scheipl S, Schöffski P, Sleijfer S, Strauss D, Strauss SJ, Sundby Hall K, Trama A, Unk M, van de Sande MAJ, van der Graaf WTA, van Houdt WJ, Frebourg T, Gronchi A & Stacchiotti S, on behalf of the ESMO Guidelines Committee, EURACAN and GENTURIS

Ann Oncol 2021;33:20-33.

https://www.annalsofoncology.org/article/S0923-7534(21)04480-X/fulltext

ESMO GUIDE TO EVALUATION OF DATA

ESMO POCKET GUIDELINES PROVIDE YOU WITH A CONCISE SUMMARY OF THE FUNDAMENTAL RECOMMENDATIONS MADE IN THE PARENT GUIDELINES IN AN EASILY ACCESSIBLE FORMAT.

This quick reference booklet provides you with the most important content of the full ESMO Clinical Practice Guidelines (CPGs) on the management of sarcomas (bone, soft tissue and visceral sarcomas) and gastrointestinal stromal tumours (GISTs). Key content includes diagnostic criteria, staging of disease, treatment plans and follow-up. The ESMO CPGs on sarcomas and GIST are intended to provide you with a set of recommendations for the best standards of care for sarcomas and GIST, using evidence-based medicine. Implementation of ESMO CPGs facilitates knowledge uptake and helps you to deliver an appropriate quality of focused care to your patients.

The approval and licensed indication of drugs mentioned in this pocket guideline may vary in different countries. Please consult your local prescribing information. This booklet can be used as a quick reference guide to access key content on evidence-based management of sarcomas and GIST.

Please visit http://www.esmo.org or http://oncologypro.esmo.org to view the full guidelines.

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SOFT TISSUE AND VISCERAL SARCOMAS

MANAGEMENT IN SPECIALIST REFERENCE CENTRES

- Management of soft tissue sarcomas (STSs) should be carried out in sarcoma reference centres or tertiary paediatric oncology centres as appropriate for age

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

- In primary soft tissue tumours, magnetic resonance imaging (MRI) is the main imaging modality in the extremities, pelvis and trunk
  - Standard radiographs may be useful to rule out a bone tumour, to detect bone erosion with a risk of fracture and to show calcifications
  - Computed tomography (CT) has a role in calcified lesions, to rule out a myositis ossificans, in pleuropulmonary sarcomas and in retroperitoneal sarcomas (RPSs) where the performance is identical to MRI
  - Ultrasound may be used as first-line imaging, but if there is any suspicion for STS it should be followed by CT or MRI
- Following appropriate imaging assessment, the standard approach to diagnosis consists of multiple, core needle biopsies, possibly by using ≥ 14-16 G needles
  - The biopsy should be carried out by a surgeon or a radiologist after multidisciplinary discussion
  - Excisional biopsy is an option for < 3 cm, superficial lesions
  - When preoperative treatment is an option, radiological imaging [including [^{18F}]2-fluoro-2-deoxy-D-glucose (FDG)–positron emission tomography (PET)/CT] may be useful, in addition to pathology, in providing information that helps to estimate the malignancy grade
- Pathological diagnosis should be made by a sarcoma expert pathologist according to the 2020 World Health Organization (WHO) classification
  - A pathological expert validation is required in all cases when the original diagnosis is made outside a reference centre/network
- The pathology report following definitive surgery should include whether the tumour was intact and the status of surgical margins
  - If preoperative treatment was administered, the pathology report should include an assessment of the pathological response, even though no validated systems for pathological response assessment are available for STSs
- Pathology diagnosis should be complemented by molecular pathology, especially when:
  - The specific pathological diagnosis is doubtful

- The clinical pathological presentation is unusual
- It may have prognostic and/or predictive relevance, as exemplified by neurotrophic tyrosine receptor kinase *(NTRK)* rearrangement
- The labels of the entity specifically refer to a distinctive molecular aberration

STAGING AND RISK ASSESSMENT

- Available staging classifications have limited relevance and should be improved
- Validated nomograms are available, which can help personalise risk assessment and aid clinical decision making, especially regarding the benefit of adjuvant/neoadjuvant treatments
- A CT scan of the thorax is recommended for staging purposes
- A CT scan of the abdomen and pelvis is recommended in the majority of sarcoma types
  - Alternatively, a whole-body MRI can also be considered
- Imaging of the brain (MRI preferred over CT) should be carried out in alveolar soft part sarcoma (ASPS) and can be considered for clear-cell sarcoma (CCS) and angiosarcoma
- FDG–PET/CT is indicated as a problem-solving tool in equivocal cases
- The surgical report should provide details on preoperative and intraoperative diagnosis, the surgical conduct, including possible contamination/tumour rupture, completeness and planned quality of margins

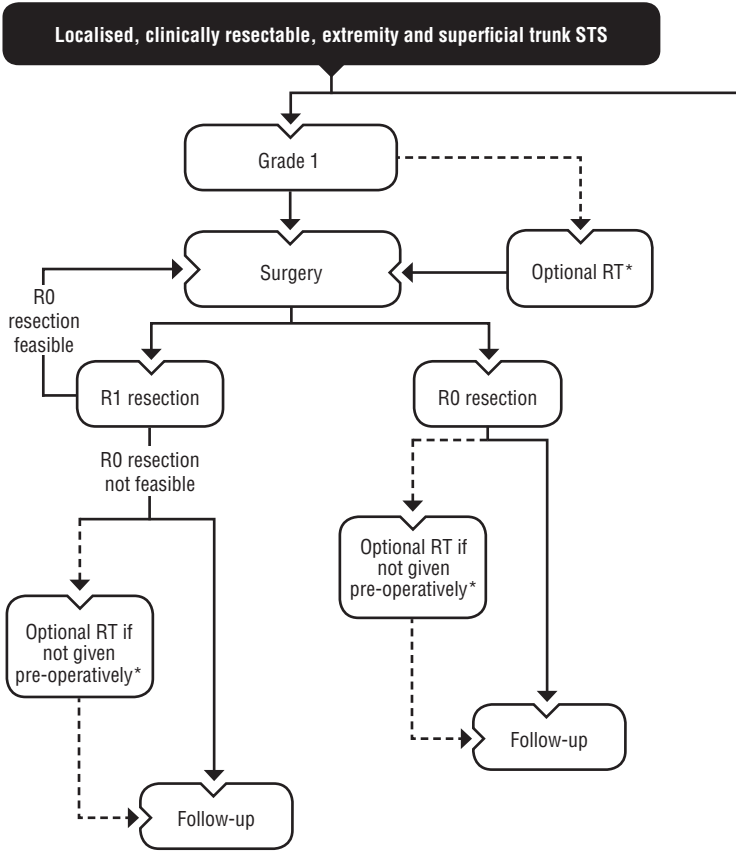
Germline *TP53* testing

- *TP53* testing should be carried out, if possible, prior to treatment start in selected patients with STS matching available criteria
- In *TP53* carriers, radiotherapy (RT) should be avoided, if possible, after multidisciplinary discussion

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

- Management of local/locoregional disease located in an extremity or superficial trunk is summarised in the figures on the following pages

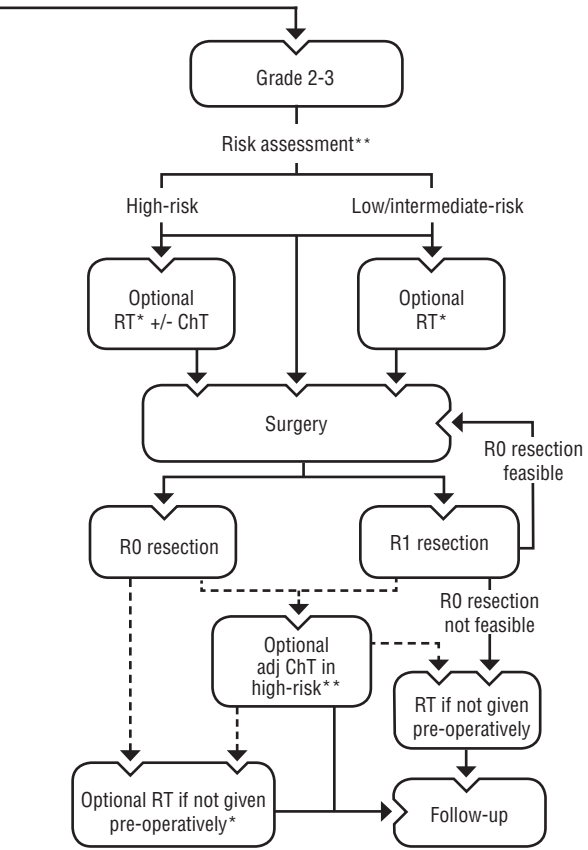
MANAGEMENT OF LOCALISED, CLINICALLY RESECTABLE, EXTREMITY AND SUPERFICIAL TRUNK STS



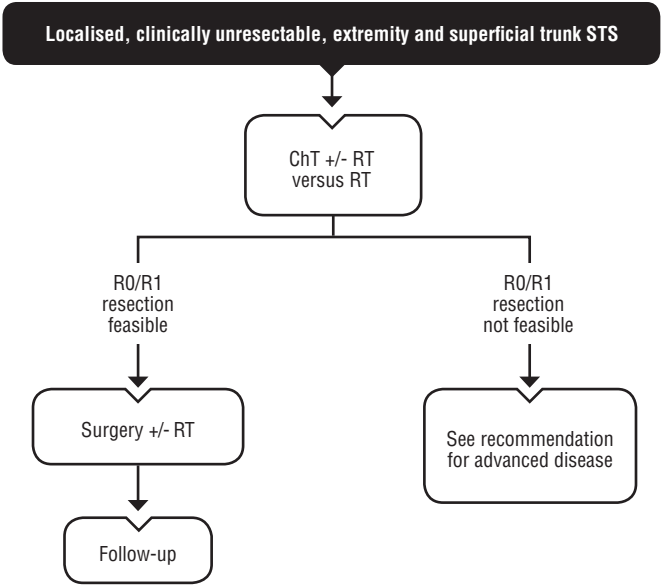
*Depending upon histology and anatomical location

**See text of full guideline

adj, adjuvant; ChT, chemotherapy; R0, no residual tumour at the margin; R1, microscopic residual tumour at the margin; RT, radiotherapy; STS, soft tissue sarcoma


Grade 2-3
Risk assessment**
High-risk
Low/intermediate-risk
Optional RT* +/- ChT
Optional RT*
Surgery
R0 resection feasible
R0 resection
R1 resection
R0 resection not feasible
Optional adj ChT in high-risk**
RT if not given pre-operatively
Optional RT if not given pre-operatively*
Follow-up

MANAGEMENT OF LOCALISED, CLINICALLY UNRESECTABLE, EXTREMITY AND SUPERFICIAL TRUNK STS



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

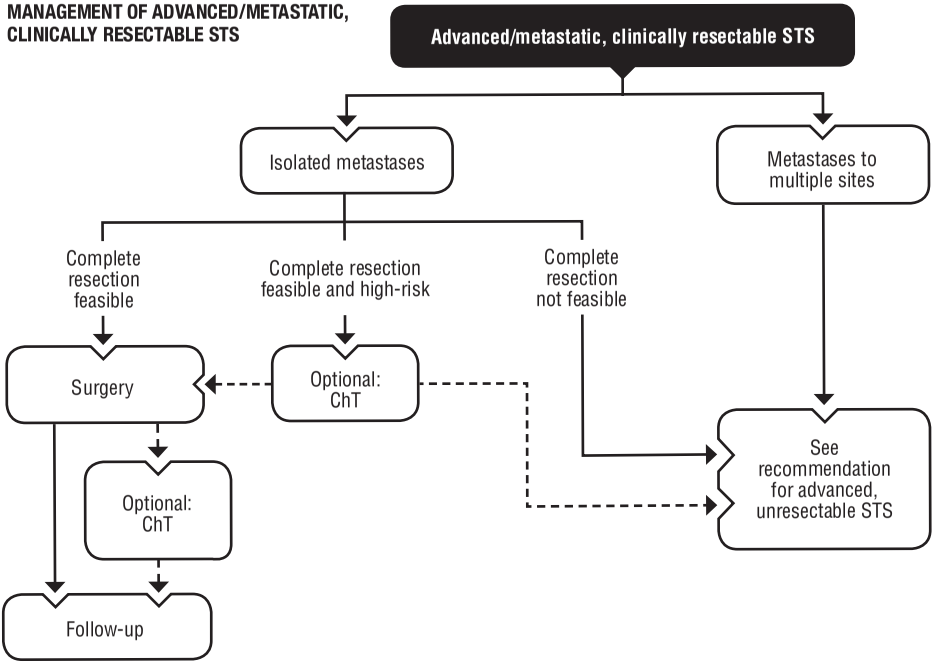
- Surgery is the standard treatment for all patients with an adult-type, localised STS and must be carried out by a surgeon specifically trained in the treatment of this disease within a sarcoma reference centre/network
- The standard surgical procedure is an *en bloc* excision with no residual tumour at the margin (R0)
- Low-grade STS are mostly treated with surgery alone
- RT is typically added to surgery as part of the standard treatment of high-grade (G2-3) lesions and it is often delivered in the preoperative setting

- Histological types such as myxoid liposarcoma, solitary fibrous tumour (SFT), myxofibrosarcoma and extraskeletal myxoid chondrosarcoma gain the greatest benefit from RT
- Re-excision at reference centres must be considered in case of unplanned resection if adequate margins can be achieved without major morbidity
- In case of surgery with macroscopic residual tumour at the margin (R2), re-excision at reference centres is mandatory, possibly following preoperative treatments if adequate margins cannot be achieved or if surgery is mutilating
  - If re-excision is not possible, post-operative RT should be considered
- Options for limb-preserving surgery include chemotherapy (ChT) and/or RT, isolated limb perfusion (ILP) with tumour necrosis factor-α plus melphalan or perioperative regional hyperthermia combined with ChT
- Adjuvant/neoadjuvant anthracycline plus ifosfamide (AI) ChT for at least three cycles can be proposed to patients at high risk of death
  - Histological types known to be refractory to AI ChT in the metastatic setting (such as ASPS or CCS) should not receive adjuvant/neoadjuvant ChT
- Neoadjuvant ChT with regional hyperthermia is another individualised option in patients at high risk of death

MANAGEMENT OF ADVANCED DISEASE

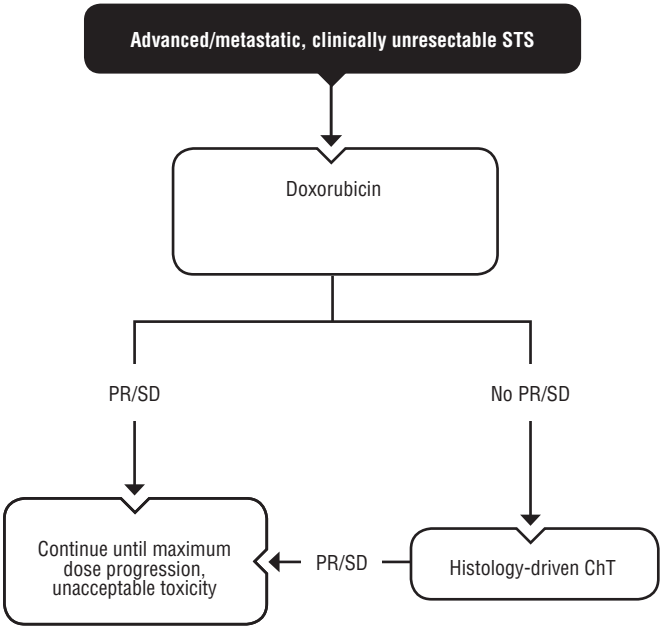
- Management of local/locoregional disease located in an extremity or superficial trunk is summarised in the figures on the following pages

MANAGEMENT OF ADVANCED/METASTATIC, CLINICALLY RESECTABLE STS



ChT, chemotherapy; STS, soft tissue sarcoma

MANAGEMENT OF ADVANCED/METASTATIC, CLINICALLY UNRESECTABLE STS



ChT, chemotherapy; DTIC, dacarbazine; PR, partial response; SD, stable disease; STS, soft tissue sarcoma

- Metachronous (disease-free interval ≥ 1 year), resectable lung metastases without extrapulmonary disease are managed with surgery as standard treatment, if complete excision of all lesions is feasible
  - When surgery of lung metastases is selected, an abdominal CT scan and a bone scan or FDG–PET are mandatory to confirm that lung metastases are 'isolated'
- ChT may be added to surgery as an option, taking into account the prognostic factors
  - ChT is preferably given before surgery to assess tumour response and modulate treatment

- When lung metastases are synchronous, in the absence of extrapulmonary disease, standard treatment is ChT
  - Surgery for resectable residual lung metastases may be offered as an option after ChT, especially when a tumour response is achieved
  - In cases of isolated lung metastases, other local treatments, such as stereo-ablative RT, may also be considered
- Pulmonary non-resectable disease and extrapulmonary metastatic disease are treated with ChT as the standard of care
  - Surgery or stereo-ablative RT of extrapulmonary metastases without ChT may be an option in selected cases, especially oligometastatic disease
  - Surgery or RT of responding metastases may be offered as an option, taking into consideration the site, tumour extent and natural history of the disease in the individual patient
- In patients with locally advanced/metastatic, nonresectable disease, systemic treatment with an essentially palliative intent can be proposed
- Anthracycline-based therapy is the standard first-line treatment
  - Multi-agent ChT with adequate-dose AI may be the treatment of choice, particularly in histological types sensitive to ifosfamide, when a tumour response is felt to be potentially advantageous and patient performance status is good
  - Doxorubicin plus dacarbazine is an option for multi-agent, first-line ChT for leiomyosarcoma (LMS), in which the activity of ifosfamide is far less convincing, and for SFT
- Angiosarcoma is highly sensitive to taxanes, which can be a treatment option in this histological type
  - An alternative option is gemcitabine, alone or in combination with docetaxel
- Imatinib is standard first-line medical therapy for patients with advanced dermatofibrosarcoma protuberans (DFSP)
- NTRK inhibitors (larotrectinib and entrectinib) are the standard treatment for those rare patients with locally advanced or metastatic *NTRK*-rearranged sarcomas
  - This treatment can also be considered in the preoperative setting, when a cytoreduction can improve morbidity and function
- Further-line systemic therapy can be considered in fit patients with advanced STS and disease progression
  - In general, patients with pre-treated advanced STS should be considered for clinical trials
  - Trabectedin is an option in advanced STS in second and further lines of treatment

- Pazopanib is an option in non-adipogenic STS in second and further lines of treatment
- Eribulin is an option in patients with liposarcomas
- The combination of dacarbazine/gemcitabine or gemcitabine/docetaxel is an option in doxorubicin-pretreated patients

FOLLOW-UP

- There are few published data to indicate the optimal routine follow-up policy of surgically-treated patients with localised disease
  - A practical approach in place at several institutions is as follows: After completion of treatment, intermediate-/high-grade patients may be followed every 3-4 months in the first 2-3 years, then twice a year up to the fifth year, and once a year thereafter; low-grade sarcoma patients may be followed every 6 months for the first 5 years, then annually

SPECIAL PRESENTATION AND ENTITIES

Retroperitoneal sarcoma

- Pre-treatment biopsy for pathological diagnosis should be carried out to allow tailored therapeutic decisions, unless otherwise indicated by the multidisciplinary board
- Comprehensive imaging evaluation is critical to accurately assess the extent of the tumour
  - Specific appreciation of the well-differentiated versus the dedifferentiated component(s) of liposarcoma is critical to surgical decision making
- The standard treatment of primary lesions is surgery through *en bloc* resection with adherent structures
- Neoadjuvant treatment, in the form of ChT, external beam RT, regional hyperthermia or combinations, can be considered in the case of technically unresectable/borderline resectable cases, and in chemosensitive histologies
- Preoperative RT can be discussed in patients with a low-intermediate grade liposarcoma
- The value of adjuvant/neoadjuvant ChT is not established

Uterine sarcomas

- Uterine sarcomas include LMS, endometrial stromal sarcomas (ESSs, formerly low-grade ESSs), undifferentiated endometrial sarcomas (UESs) and adenosarcoma with sarcomatous overgrowth (ASS)
- Standard local treatment of localised uterine LMS (U-LMS), ESS and UES is *en bloc* total hysterectomy (including laparoscopy/assisted or robotic surgery, provided the tumour is resected with the same criteria as for open surgery and morcellation is not carried out)

- Systematic lymphadenectomy has not been demonstrated to be useful
- Adjuvant RT and ChT are not regarded as standard treatment

- The systemic treatment of advanced U-LMS, UES and ASS parallels that for adult-type STSs
  - As for all LMSs, doxorubicin, dacarbazine, trabectedin, gemcitabine alone or in combination with docetaxel and pazopanib are active agents and may be used in a stepwise fashion
- The systemic treatment of metastatic low-grade ESSs exploits their sensitivity to hormonal therapy (HT)
  - Therefore, progestins, aromatase inhibitors and gonadotropin-releasing hormone analogues (for premenopausal patients) can be used
  - ChT may be an option when HT has failed
- For benign metastasising leiomyomas, clinical observation is the treatment of choice at diagnosis, with HT (as for ESS) being standard treatment of progressing disease and surgery
- The same applies to peritoneal leiomyomatosis if non-mutilating surgery is not feasible
- For pelvic aggressive angiomyxoma, surgery may be the treatment of choice if not debilitating, with observation thereafter

Desmoid-type fibromatosis

- Active surveillance is the first-line strategy for all newly diagnosed primary desmoid-type fibromatosis (DF), without life-threatening presentations
- The preferred imaging modality is MRI
- For progressive disease, the optimal strategy needs to be individualised on a multidisciplinary basis and may consist of further watchful waiting, systemic therapies or local therapies such as percutaneous cryoablation (extra-abdominal cases), ILP (if the lesion is confined to an extremity) and surgery in favourable locations (i.e. abdominal wall)
- Definitive RT should be considered after multiple failed lines of treatment or for tumours in critical anatomical locations where surgery would involve prohibitive risk or functional impairment, especially in elderly patients
- When a systemic therapy is chosen, available options include low-dose ChT, sorafenib, pazopanib, imatinib and full-dose ChT (using regimens active in sarcomas, including liposomal doxorubicin)
  - The value of HT is poorly defined

Breast sarcomas

- Patients should be referred to sarcoma units and managed jointly within breast units
- In general, breast-conserving surgery may be carried out, depending on the quality of margins versus the size of the tumour and the breast, along with the feasibility of RT in primary breast sarcoma, while wide excision of the RT field and immediate plastic surgical reconstruction is often necessary in radiation-induced breast sarcoma
- In angiosarcomas of the mammary gland the tendency to recur is high and mastectomy (involving the muscular fascia and the whole previously irradiated field) is recommended in most cases, even in combination with post-operative RT
  - Considering the high risk of angiosarcoma to develop local and systemic relapses, preoperative treatments including ChT and RT may be used

SUMMARY RECOMMENDATIONS FOR SOFT TISSUE AND VISCERAL SARCOMAS

MANAGEMENT IN SPECIALIST REFERENCE CENTRES

Management of STSs should be carried out in sarcoma reference centres or tertiary paediatric oncology centres as appropriate for age

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

In primary soft tissue tumours, MRI is the main imaging modality in the extremities, pelvis and trunk

Following appropriate imaging assessment, the standard approach to diagnosis consists of multiple, core needle biopsies

Pathological diagnosis should be made by a sarcoma expert pathologist according to the 2020 WHO classification

Pathology diagnosis should be complemented by molecular pathology

STAGING AND RISK ASSESSMENT

Available staging classifications are of limited clinical value; risk assessment is better obtained through the available nomograms

Staging is routinely carried out with contrast-enhanced chest, abdomen and pelvis CT

- Whole-body MRI may be an alternative, especially in selected histotypes
- Brain CT/MRI may be indicated only in ASPS, CCS and angiosarcoma
- FDG–PET/CT is indicated as a problem-solving tool in equivocal cases

The surgical report should include preoperative and intraoperative diagnosis, possible contamination/tumour rupture, completeness and planned quality of microscopic margins

TP53 testing should be carried out in selected patients with STS under the age of 46 years

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

Surgery is the standard treatment for all patients with an adult-type, localised STS and must be carried out by a surgeon specifically trained in the treatment of this disease within a sarcoma centre/network

- The standard surgical procedure is an *en bloc* excision with R0 margins
- Wide excision and RT are the standard treatment of high-grade (G2-3) lesions
- The sequence of the two treatments varies among institutions, but there is an overall shift towards the use of preoperative RT, especially when preserving a critical structure is one of the goals

Options for limb-preserving surgery include ChT and/or RT, or ILP or regional hyperthermia combined with ChT

In patients at high risk of death:

- Adjuvant/neoadjuvant AI ChT for at least three cycles can be proposed
- Neoadjuvant ChT with regional hyperthermia is another individualised option

MANAGEMENT OF ADVANCED DISEASE

Standard treatment of metachronous (disease-free interval ≥ 1 year), resectable lung metastases without extrapulmonary disease is surgery, if complete excision of all lesions is feasible

Standard ChT is based on anthracyclines as first-line treatment

- Multi-agent ChT with adequate-dose AI or dacarbazine may be the treatment of choice, particularly in subtypes sensitive to ifosfamide or dacarbazine, when a tumour response is felt to be potentially advantageous and patient performance status is good

Gemcitabine/docetaxel is not generally recommended as a first-line therapy for advanced STS patients

Imatinib is standard medical therapy for patients with DFSP

NTRK inhibitors are standard treatment of patients with advanced *NTRK*-rearranged sarcomas; they can be considered also in the preoperative setting, when a cytoreduction can improve morbidity and function

Trabectedin is an option in advanced STS in second and further lines of treatment

Pazopanib is an option in non-adipogenic STS in second and further lines of treatment

Eribulin is an option in patients with liposarcomas

The combination of dacarbazine/gemcitabine or gemcitabine/docetaxel is an option in doxorubicin-pretreated patients

FOLLOW-UP

A practical approach in place at several institutions is as follows: After completion of treatment, intermediate-/high-grade patients may be followed every 3-4 months in the first 2-3 years, then twice a year up to the fifth year, and once a year thereafter; low-grade sarcoma patients may be followed every 6 months for the first 5 years, then annually

SPECIAL PRESENTATION AND ENTITIES

Patients with suspected RPS, uterine sarcoma, DF and breast sarcoma need to be referred to high-volume sarcoma centres

Standard treatment of RPS consists of surgical resection *en bloc* with adherent organs

SUMMARY RECOMMENDATIONS (CONT'D)

Neoadjuvant RT has shown signs of efficacy in primary low-/intermediate-grade retroperitoneal liposarcoma

Intraoperative/post-operative RT is of no proven value in RPS; the role of adjuvant/neoadjuvant ChT is not yet established

Standard local treatment of localised U-LMS, ESSs and UESs is *en bloc* total hysterectomy; adjuvant RT and ChT are not regarded as standard treatment

Active surveillance is the first-line strategy for all newly diagnosed primary DF, without life-threatening presentations

For progressing DF, the optimal strategy needs to be individualised on a multidisciplinary basis and may even consist of the continuation of the active surveillance, systemic therapies, local therapies, such as percutaneous cryoablation, ILP (if the lesion is confined to an extremity), surgery in favourable locations or RT

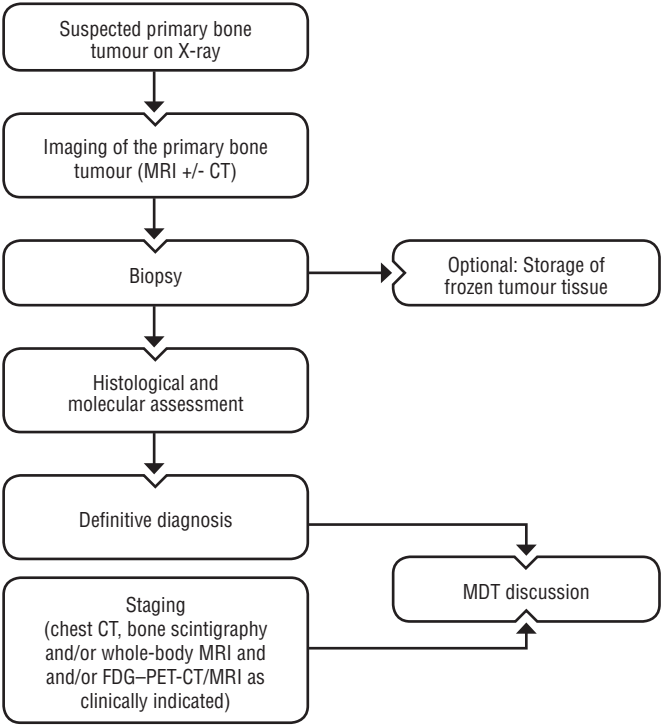
BONE SARCOMAS

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

Diagnosis

- A general diagnostic strategy for bone sarcoma is shown in the figure below

GENERAL DIAGNOSTIC STRATEGY FOR BONE SARCOMAS



CT, computed tomography; FDG–PET, [^{18}]2-fluoro-2-deoxy-D-glucose–positron emission tomography; MDT, multidisciplinary team; MRI, magnetic resonance imaging

- The initial work-up of a suspected primary bone sarcoma tumour should be carried out at a sarcoma reference centre, and should include medical history, physical examination, radiological assessment and biopsy
- The presence of persistent and often progressive nonmechanical bone pain, predominantly at night, should prompt a radiological assessment
  - Conventional radiography in two planes is the first radiological investigation
- When the diagnosis of malignancy cannot be definitely excluded on radiographs, magnetic resonance imaging (MRI) of the whole compartment with adjacent joints should be carried out
  - MRI is currently regarded as the best modality for local staging for tumours of the extremities, spine and pelvis
  - Computed tomography (CT) may provide additional information on bone involvement (presence of calcification, periosteal bone formation and cortical destruction) and can be chosen as the preferred imaging modality for other primary sites
- All patients with a bone lesion which is suspected to be a primary bone sarcoma on a radiological basis should be referred to a bone sarcoma reference centre or to an institution belonging to a sarcoma network
  - Children and adolescents should be referred to centres that, in addition, provide age-specific expertise

Pathology and molecular biology

- Pathological diagnosis should be made by a bone tumour expert dedicated pathologist according to the 2020 World Health Organization (WHO) classification and should be supported by ancillary investigations whenever relevant
- The biopsy of a suspected primary bone sarcoma should be carried out by either the surgical team who will carry out the definitive tumour resection or by a dedicated interventional radiologist after discussing with the surgeon
  - For those patients whose pathological diagnosis was obtained outside a reference network, an expert pathological review in a sarcoma reference centre is mandatory
  - In most patients, a core needle biopsy, taken under imaging guidance, represents an appropriate alternative to open biopsy
- Histology specimens must be interpreted by an experienced bone tumour pathologist, in collaboration with the radiologist, and discussed in a multidisciplinary team (MDT)
  - The collection of fresh snap-frozen tissue is encouraged to overcome damage to nucleic acids resulting from decalcification, and to allow subsequent molecular assessment

- For surgical specimens, tumour size and local extent of spread, site, status of surgical margins and percentage of pathological response to preoperative chemotherapy (ChT) should be described

STAGING AND RISK ASSESSMENT

- Tumour burden and the presence of detectable metastases are the two main factors taken into consideration in the clinical staging of these diseases
- General staging should be carried out to assess the extent of distant disease, including bone scintigraphy and dedicated chest CT
  - Whole-body (WB)-MRI and [^{18F}]2-fluoro-2-deoxy-D-glucose (FDG)–positron emission tomography (PET)-CT or PET-MRI are increasingly utilised for staging of bone and bone marrow metastases (including skip bone lesions)
  - Additional appropriate imaging studies and biopsies can be taken from suspicious sites
- Baseline serum analysis in Ewing sarcoma and osteosarcoma should include alkaline phosphatase (AP) and lactate dehydrogenase (LDH) given their proven prognostic value and their use as response monitoring during treatment
- Before starting ChT, baseline renal function testing, assessment of cardiac function and an audiogram (in the case of platinum derivatives) should be carried out
- Sperm storage is recommended for male patients of reproductive age
- For female patients, consultation with a fertility physician about potential ovarian sampling, cryopreservation, use of gonadotrophin-releasing hormone agonists and other means of ovarian suppression for fertility preservation should be considered, where available

Germline *TP53* testing in osteosarcoma

- The criteria for germline *TP53* testing in patients with osteosarcoma are shown in the table on the next page

CRITERIA FOR GERMLINE *TP53* TESTING IN OSTEOSARCOMA PATIENTS

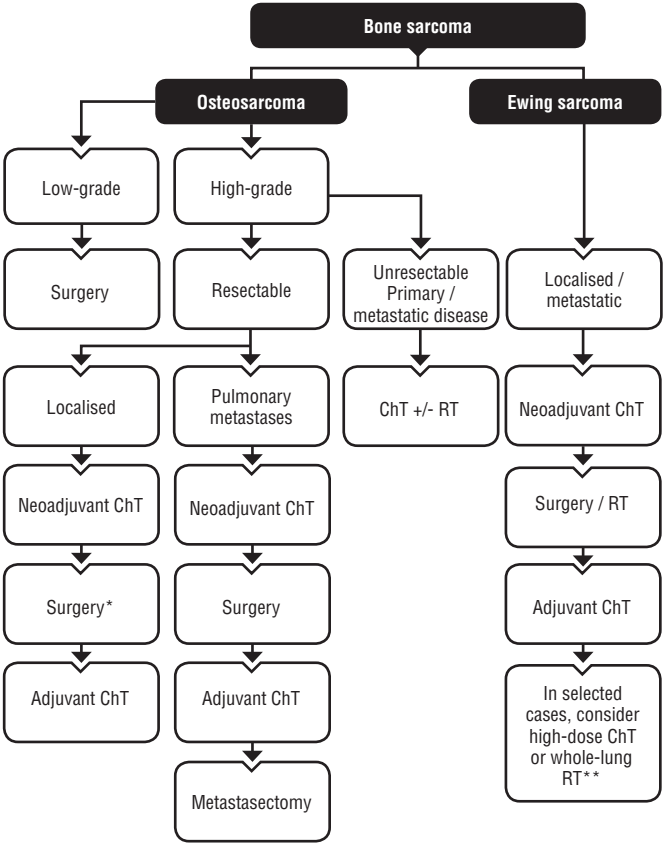
PRESENTATION	CRITERIA
Familial presentation	Patient with osteosarcoma before 46 years of age AND at least one first- or second-degree relative with a *TP53* core tumour (breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumour, adrenocortical carcinoma) before 56 years of age
Multiple primitive tumours	Patient with osteosarcoma and another *TP53* core tumour, the first of which occurred before 46 years of age, irrespective of family history

Frebourg T et al. Eur J Hum Genet 2020;28:1379-86. Adapted under a Creative Commons license.

TREATMENT

- Given their rarity and the complexity of management, the accepted standard for bone sarcoma is treatment at reference centres and/or within reference networks able to provide access to the full spectrum of care and age-specific expertise
- The principles for the treatment of osteosarcoma and Ewing sarcoma are summarised in the figure on the next page

GENERAL THERAPEUTIC STRATEGY FOR OSTEOSARCOMA AND EWING SARCOMA



*Surgery can be offered upfront, followed by adjuvant ChT
**See section on Ewing sarcoma under Treatment section
ChT, chemotherapy; RT, radiotherapy

Osteosarcoma

- Low-grade central and parosteal osteosarcoma are malignancies with a low metastatic potential that should be treated by surgery alone
- Curative treatment of high-grade osteosarcoma consists of ChT and surgery

Surgery

- Surgery should be carried out by a surgical team familiar with the wide range of surgical reconstructions
  - Paediatric and adolescent patients need to be treated by surgeons with experience in the field of paediatric bone tumours, including age-specific reconstruction challenges, such as the reconstruction of growing bones
  - Most patients should be considered candidates for limb salvage
- Clear margins are the first goal of surgery
  - Resection with microscopic (R1) and macroscopic (R2) residual tumour at the margin both increase the local recurrence rate, which is associated with reduced overall survival (OS)
  - Areas where there is suspicion of close margins should be marked on the surgical specimen sent to pathology
- In cases of fracture, internal fixation is contraindicated as it disseminates the tumour further into both bone and soft tissues and increases the risk of local recurrence; external splintage is recommended
  - Pathological fracture does not necessarily require an amputation
  - Primary neoadjuvant ChT can be used with the expectation that it will allow the fracture haematoma to contract and allow subsequent resection of the tumour and the involved soft tissues

ChT

- Most current protocols for localised disease include a period of preoperative ChT
- Doxorubicin, cisplatin, high-dose methotrexate (HD-MTX) and ifosfamide have antitumour activity in osteosarcoma
  - The doxorubicin/cisplatin/HD-MTX (MAP) regimen is most frequently used as front-line ChT in children and young adult patients
  - In patients > 40 years, regimens combining doxorubicin, cisplatin and ifosfamide are an alternative
- Muramyl tripeptide (MTP) has been approved in Europe for patients < 30 years of age with completely resected localised osteosarcoma; however, there is no consensus for its use within the sarcoma community

Radiotherapy

- Radiotherapy (RT) may be considered in osteosarcoma patients with unresectable primary tumours where surgery would be unacceptably morbid, or as adjuvant treatment of tumours at high risk of local recurrence and with limited option for further surgery
- Modern RT techniques [including heavy particles and intensity-modulated RT (IMRT)] may offer a technical advantage to deliver high doses and should be considered where appropriate, especially in paediatric patients or young adults

High-grade craniofacial osteosarcoma

- High-grade craniofacial osteosarcoma should be treated the same way as high-grade osteosarcoma of other sites, although the value of ChT in this setting is still not clearly defined
  - In this location, RT can be proposed when complete surgery is not feasible and in patients undergoing resection with positive margins; modern RT techniques (including heavy particles and IMRT) can be considered

Primary metastatic osteosarcoma

- Primary metastatic osteosarcoma patients are treated with a curative intent following the same principles of non-metastatic osteosarcomas
- MTP does not offer a survival benefit in this group

Recurrent osteosarcoma

- The treatment of recurrent osteosarcoma is primarily surgical in the case of isolated lung metastases or local recurrence
  - Complete removal of all resectable metastases must be attempted, as more than one third of patients with a complete second surgical remission survive > 5 years
  - Even patients with subsequent recurrences may be cured as long as recurrences are resectable, and repeated thoracotomies are often warranted
  - For lung metastases, stereotactic RT, radiofrequency ablation (RFA) or cryotherapy might be used as alternative options in patients unfit for surgery
  - Some groups also consider RFA and stereotactic RT as potentially alternative local treatment options for bone metastases
- Second-line ChT for recurrent osteosarcoma includes ifosfamide or cyclophosphamide, possibly in association with etoposide and/or carboplatin, and other active drugs including gemcitabine and docetaxel

Extra-osseous osteosarcoma

- Extra-osseous osteosarcoma is exceedingly rare, and there is no consensus about whether treatment should be in accordance with skeletal osteosarcoma or STSs

Ewing sarcoma

- Ewing sarcoma is a round cell sarcoma (RCS), marked by a gene fusion involving a member of the FET family (usually *EWSR1*) and a member of the ETS family of transcription factors
- Molecular confirmation is mandatory for the distinction between Ewing sarcoma and other RCSs
- Staging must be carried out to detect lung, bone and bone marrow metastases and should include biopsy in case of doubtful lesions
  - FDG–PET-CT or WB-MRI are preferred over bone scan for skeletal imaging, if available
  - Bone marrow biopsies and aspirates (from sites distant to the primary or known metastatic lesions) are not mandated if an FDG–PET-CT is done

ChT

- The interval-compressed vincristine/doxorubicin/cyclophosphamide/ifosfamide/etoposide (VDC/IE) regimen is currently the preferred first-line treatment in Ewing sarcoma
- The use of busulfan/melphalan (BuMel) could be considered for selected patients with poor response to vincristine/ifosfamide/doxorubicin/etoposide (VIDE) induction ChT and/or tumour volume > 200 ml
- For poor-responding patients treated with interval-compressed VDC/IE, the role of high-dose ChT has not been evaluated
  - The selection of the most appropriate consolidation should take into account the ChT regimen received and need for RT

Surgery

- Complete surgical excision, where feasible, is regarded as the best modality of local control, given the higher risk of local recurrence when RT is used as the sole treatment
  - Surgery must involve excision of all tissues originally involved before induction ChT (not only the tumour tissue remaining following dimensional shrinkage on ChT)
  - Intralesional surgery must be avoided, as there is no benefit compared with RT alone

RT

- RT with definitive intent alone should be used instead of surgery if complete surgical excision is not possible and in cases with challenging local sites, such as axial or spinal tumours, where surgery will be unacceptably morbid
- Adjuvant RT (45-60 Gy) should be recommended in patients with large volume tumours (> 200 ml), poor histological response or inadequate surgical margins
  - It should be considered in patients with non-sacral pelvic Ewing sarcoma regardless of surgical margins, tumour volume or histological response

Primary metastatic and recurrent Ewing sarcoma

- Patients with metastases at diagnosis are treated with the same treatment approach as patients with localised disease, but have a worse prognosis
- ChT regimens for relapsed Ewing sarcoma are not standardised and include alkylating agents (cyclophosphamide and ifosfamide) in combination with topoisomerase inhibitors (etoposide and topotecan), irinotecan with temozolomide, gemcitabine and docetaxel, high-dose ifosfamide or carboplatin with etoposide
- For selected patients with a long disease-free interval of 2 years achieving a complete remission through medical therapy and/or surgery, consolidation with high-dose ChT may be considered

Extraskeletal Ewing sarcoma

- Treatment of patients with extraskeletal Ewing sarcoma follows the same principles as for bone Ewing sarcoma, thus incorporating ChT in all cases as well as RT in most cases
- Given their favourable prognosis, the number of cycles in cutaneous and subcutaneous Ewing sarcoma is to be discussed case by case, at an MDT level and with the patient

RCSs with *EWSR1* non-ETS fusions, *CIC*-rearranged sarcoma and sarcoma with *BCOR* alterations

- RCS with *EWSR1* non-ETS fusions, *CIC*-rearranged sarcoma and sarcoma with *BCOR* alterations are currently recognised as distinct entities, with distinctive molecular, immunohistochemical, clinical and epidemiological features
- There is no consensus on whether they should be treated with an Ewing sarcoma-like approach or regarded as high-grade soft tissue sarcoma
- When feasible, combination regimens including anthracycline and alkylating agents should be favoured
- Registration within clinical trials and prospective registries is recommended

Chondrosarcoma

- The majority of conventional chondrosarcomas are locally aggressive or low-grade, non-metastasising tumours (atypical cartilaginous tumour/ chondrosarcoma grade I), rather than high-grade chondrosarcoma (grades II-III)
- Atypical cartilaginous tumours in the long bones of the limbs can be managed by curettage with or without local adjuvant therapy (e.g. phenol, cement and cryotherapy)
  - Alternatively, some reference centres now recommend active surveillance, with close radiological monitoring, for progressive and asymptomatic lesions
- Low-grade peripheral chondrosarcomas (arising from osteochondromas) should be surgically excised, aiming to excise the tumour with a covering of normal tissue over it
- Higher-grade chondrosarcomas (grade II-III) and all chondrosarcomas of the pelvis or axial skeleton should be surgically excised with wide margins
- RT can be considered for unresectable disease (primary or recurrent), after incomplete surgery and for symptoms palliation
- High-dose RT is currently recommended for patients with skull base chondrosarcomas
- Localised mesenchymal chondrosarcomas (MCSs) are usually treated with adjuvant/neoadjuvant ChT combining anthracycline and alkylating agents
- Adjuvant/neoadjuvant ChT can also be considered for localised dedifferentiated chondrosarcoma (DCS)
- For patients with oligometastatic, resectable lung disease, surgery, RT or local ablation can be considered, especially for conventional chondrosarcomas
- In patients with widely metastatic disease, ChT is of limited benefit, with higher responses seen in patients receiving combination anthracycline-based therapy and those with DCS or MCS; the activity of gemcitabine and docetaxel has been reported

Chordoma

- Conventional chordoma is marked by nuclear expression of brachyury and its diagnostic assessment is highly recommended
- *En bloc* resection with no residual tumour at the margin (R0) is the recommended treatment of primary localised disease when feasible and sequelae are accepted by the patient
- For sacral chordoma, surgery should be offered as a first choice in case of lesions arising from levels of sacral spinal nerve 4 (S4) and below, or discussed in the context of other alternatives for tumours originating above sacral spinal nerve 3 (S3)

- R1-R2 surgery plus high-dose RT is the treatment of choice for skull base and upper cervical tract chordoma
- Adjuvant RT should always be considered for skull base and cervical spine chordomas, and for sacral and mobile spine chordoma with R1 resection margins
- If *en bloc* R0 resection is not feasible, the patient is inoperable or surgical sequelae are unacceptable to the patient, definitive RT alone (without debulking) is an alternative
- In the case of local recurrence, possible salvage treatment can include surgery and/or RT and/or RFA and/or cryotherapy and/or systemic treatment, balancing morbidity, quality of life and expected disease control
- For oligometastatic disease, surgery, RFA, cryotherapy or stereotactic RT can be considered in selected cases
- ChT is inactive and is generally not recommended

Giant cell tumour of bone

- Giant cell tumour of bone (GCTB) is a locally aggressive, rarely metastatic tumour, typically affecting the end of long bones, but also arising in the axial skeleton, especially from sacrum or vertebral bodies
- Treatment options include intralesional curettage with or without adjuvant therapy and *en bloc* excision
- Denosumab is the standard treatment in unresectable or metastatic GCTBs
- Denosumab use in the preoperative setting for GCTBs that are potentially resectable with high morbidity is debated and should be individualised and reserved for complex cases following MDT discussion

High-grade spindle/undifferentiated pleomorphic sarcomas of bone

- Undifferentiated pleomorphic sarcomas of bone are a diagnosis of exclusion as they have no identifiable line of differentiation
  - Expert pathology review should be carried out to exclude other rare or recently described sarcoma types
- Treatment strategies mimic those of osteosarcoma, with ChT and complete *en bloc* resection including any soft tissue component
  - RT may be considered in inoperable lesions

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

- Follow-up of high-grade bone sarcoma should include a physical examination, cross-sectional imaging and plain radiograph of the primary site (or MRI or CT) together with chest X-ray/CT scan

- A recommended follow-up policy could include evaluation after the completion of ChT, approximately every 2-3 months for the first 2 years, every 6 months for years 3-5, every 6-12 months for years 5-10 and thereafter every 0.5-1-2 years according to local practice and other factors
- In the case of low-grade bone sarcoma, the frequency of follow-up visits may be lower (e.g. 6 months for 2 years and then annually)
- Long-term toxic effects of ChT, surgery and RT should be evaluated, and monitoring for late effects should be continued for > 10 years after treatment, depending on the protocol used

SUMMARY RECOMMENDATIONS FOR BONE SARCOMAS

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

Diagnosis

- The initial work-up of a suspected primary bone sarcoma tumour should be carried out at a sarcoma reference centre, and should include medical history, physical examination, radiological assessment and biopsy

Pathology and molecular biology

- Pathological diagnosis should be made by a bone tumour expert dedicated pathologist according to the 2020 WHO classification and should be supported by ancillary investigations whenever relevant
- For surgical specimens, tumour size and local extent of spread, site, status of surgical margins and percentage of pathological response to preoperative ChT should be described

STAGING AND RISK ASSESSMENT

General staging should be carried out to assess the extent of distant disease, including chest CT, bone scintigraphy and/or WB-MRI and/or FDG–PET-CT/MRI as clinically indicated

- Baseline serum analysis in Ewing sarcoma and osteosarcoma should include AP and LDH levels

TREATMENT

Given their rarity and the complexity of management, the accepted standard for bone sarcoma is treatment at reference centres and/or within reference networks able to provide access to the full spectrum of care and age-specific expertise

Osteosarcoma

- Low-grade central and parosteal osteosarcoma are malignancies with a low metastatic potential that should be treated by surgery alone
- Curative treatment of high-grade osteosarcoma consists of ChT and surgery
  - Most current protocols for localised disease include a period of preoperative ChT
- Doxorubicin, cisplatin, HD-MTX and ifosfamide have antitumour activity in osteosarcoma; in patients > 40 years, regimens combining doxorubicin, cisplatin and ifosfamide are an alternative

SUMMARY RECOMMENDATIONS (CONT'D)

- High-grade craniofacial osteosarcoma should be treated the same way as high-grade osteosarcoma of other sites, although the value of ChT in this setting is still not clearly defined; in this location, RT can be proposed when complete surgery is not feasible and in patients undergoing resection with positive margins
- Heavy particle RT and IMRT can be considered, particularly for unresectable primary tumours
- Primary metastatic osteosarcoma patients are treated with a curative intent following the same principles of non-metastatic osteosarcomas
  - MTP does not offer a survival benefit in this group
- The treatment of recurrent osteosarcoma is primarily surgical in the case of isolated lung metastases or local recurrence
  - RFA and stereotactic RT are potential alternative local treatment options in patients unfit for surgery and for small lung or bone metastases
- Second-line ChT for recurrent osteosarcoma includes ifosfamide or cyclophosphamide, possibly in association with etoposide and/or carboplatin, and other active drugs including gemcitabine and docetaxel

Ewing sarcoma

- Molecular confirmation is mandatory for the distinction between Ewing sarcoma and other RCSs
- The interval-compressed VDC/IE regimen is currently the preferred first-line treatment in Ewing sarcoma
- The use of BuMel could be considered for selected patients with poor response to VIDE induction ChT and/or tumour volume > 200 ml
- The role of high-dose ChT has not been evaluated with interval-compressed VDC/IE
  - The selection of the most appropriate consolidation should take into account the ChT regimen received and need for RT
- Complete surgical excision, where feasible, rather than RT as a sole modality is regarded as the best modality of local control
- Adjuvant RT (preoperative or post-operative) is indicated where the original involved tissues cannot be completely resected with adequate surgical margins, for large-volume tumours or poor histological response
  - It should be considered in patients with non-sacral pelvic Ewing sarcoma regardless of surgical margins, tumour volume or histological response

- For patients with metastases at diagnosis, ChT is similar to that for localised disease
- ChT regimens for relapsed disease include alkylating agents in combination with topoisomerase inhibitors, irinotecan with temozolomide, gemcitabine and docetaxel, high-dose ifosfamide or carboplatin with etoposide
- Treatment of patients with extraskeletal Ewing sarcoma follows the same principles as for bone Ewing sarcoma
- For cutaneous/subcutaneous Ewing sarcoma, the number of ChT cycles should be discussed on an individual case basis

RCS with *EWSR1* non-ETS fusions, *CIC*-rearranged sarcoma and sarcoma with *BCOR* alterations

- There is no consensus on whether they should be treated with an Ewing sarcoma-like approach or regarded as high-grade soft tissue sarcoma; combination regiments including anthracycline and alkylating agents should be favoured when feasible
- Registration within clinical trials and prospective registries is recommended

Chondrosarcoma

- Atypical cartilaginous tumours in the long bones of the limbs can be managed by curettage with or without local adjuvant therapy
- High-grade chondrosarcomas and all chondrosarcomas of the pelvis or axial skeleton should be surgically excised with wide margins
- RT can be considered for unresectable disease (primary or recurrent), after incomplete surgery and for symptoms palliation
- High-dose RT is currently recommended for patients with skull base chondrosarcomas
- Localised MCSs are usually treated with adjuvant/neoadjuvant ChT combining anthracycline and alkylating agents
- Adjuvant/neoadjuvant ChT can also be considered for localised DCS

Chordoma

- The assessment of brachyury nuclear expression in conventional chordoma is highly recommended to confirm diagnosis
- Surgery should be offered if the chordoma arises from S4 and below or discussed in the context of other alternatives for tumours originating above S3
- R1-R2 surgery plus high-dose RT is the treatment of choice for skull base and upper cervical tract chordoma

SUMMARY RECOMMENDATIONS (CONT'D)

- Indications for definitive RT include disease for which R0 or R1 resection cannot be achieved according to an expert centre, inoperable patients and neurological impairment not accepted by the patient
- For relapse, treatment includes surgery and/or RT and/or systemic therapies
- ChT is inactive and is generally not recommended

GCTB

- Treatment options for GCTB include *en bloc* excision and intralesional curettage with or without adjuvant therapy in carefully selected cases
- Denosumab is the standard treatment in unresectable or metastatic GCTB
- Denosumab use in the preoperative setting for GCTBs that are potentially resectable with high morbidity is debated and should be individualised and reserved for complex cases following MDT discussion

High-grade spindle/undifferentiated pleomorphic sarcomas of bone

- Treatment strategies mimic those of osteosarcoma and include ChT and complete *en bloc* resection

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Follow-up of high-grade bone sarcoma should include a physical examination, cross-sectional imaging and plain radiograph of the primary site together with chest X-ray/CT scan

A recommended follow-up policy may foresee intervals of approximately every 3 months for the first 2 years, every 6 months for years 3-5, every 6-12 months for years 5-10, and thereafter every 0.5-1-2 years

For low-grade bone sarcoma, the frequency of follow-up visits may be lower (e.g. 6 months for 2 years and then annually)

Long-term toxic effects of ChT, surgery and RT should be evaluated, and monitoring for late effects should be continued for > 10 years after treatment

GASTROINTESTINAL STROMAL TUMOURS

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

- The standard approach for patients with oesophagogastric or duodenal submucosal nodules < 2 cm is endoscopic ultrasound (EUS) assessment
  - If biopsy is feasible and a diagnosis of gastrointestinal stromal tumour (GIST) is made, resection should be performed, unless major morbidity is expected (i.e. oesophagogastric junction, second portion of the duodenum on the medial aspect)
  - If a biopsy is not feasible or results in inadequate material for diagnosis, active surveillance is generally recommended
- The standard approach to rectal nodules is represented by biopsy or excision after endorectal ultrasound assessment and pelvic magnetic resonance imaging (MRI), regardless of the tumour size and mitotic rate
- The standard approach to tumours ≥ 2 cm in size is biopsy/excision because they are associated with a higher risk of progression if confirmed as GIST
  - If there is an abdominal nodule or a mobile mass in the abdominal cavity not amenable to endoscopic assessment, laparoscopic/open excision is the standard approach
  - If there is a large mass and surgery is likely to be a multivisceral resection, multiple core needle biopsies are the standard approach, obtained through EUS guidance, or through an ultrasound/computed tomography (CT)-guided percutaneous approach
- If a patient presents with obvious metastatic disease, a biopsy of the metastatic focus (if easier to make in comparison to the primary tumour) is sufficient to establish the diagnosis and decide the treatment
- Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy as well as a prognostic relevance
  - Its inclusion in the diagnostic work-up of all GISTs should be considered standard practice (with the possible exclusion of < 2 cm nonrectal GISTs)
  - Centralisation of mutational analysis in a laboratory enrolled in an external quality assurance programme and with expertise in the disease may be useful
- Multidisciplinary treatment planning is needed involving pathologists, radiologists, surgeons, medical oncologists, as well as gastroenterologists and nuclear medicine specialists, as applicable

- Management should be carried out at reference centres for sarcomas and GISTs and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually

STAGING AND RISK ASSESSMENT

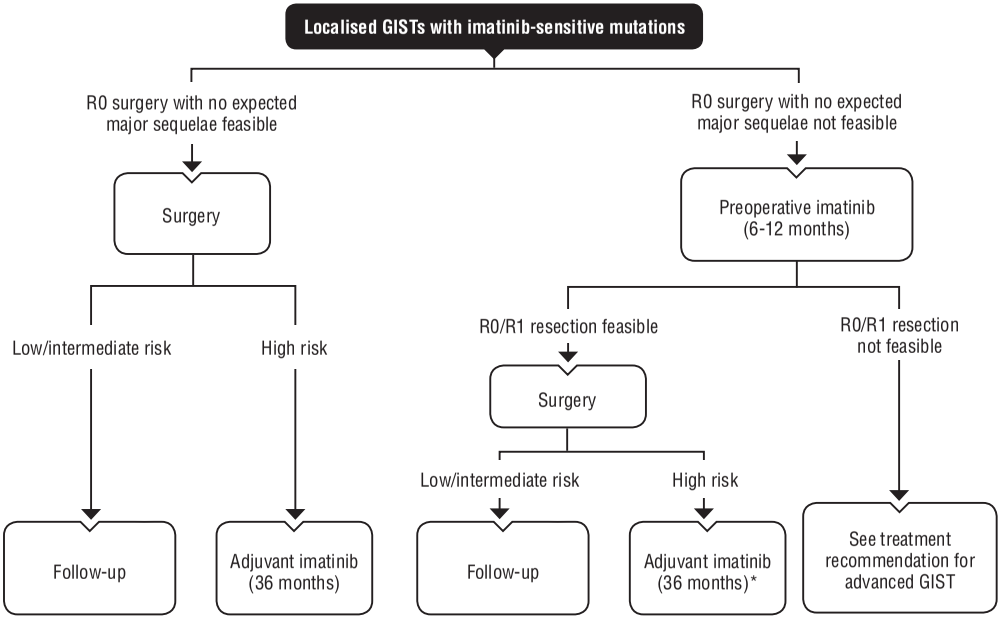
- The mitotic rate, tumour size and tumour site are important prognostic factors (gastric GISTs have a better prognosis than small bowel or rectal GISTs)
- Tumour rupture is an additional adverse prognostic factor and should be recorded, regardless of whether it took place before or during surgery
- Several risk classifications have been proposed to assess the risk of relapse of a localised disease
  - A widely used risk classification was proposed by the Armed Forces Institute of Pathology, which incorporates the primary mitotic count, tumour size and tumour site (i.e. the three main prognostic factors in localised GISTs)
  - A nomogram utilising all three criteria has been developed on another series
- Staging procedures are selected considering that most relapses affect the peritoneum and the liver
- Triple phase contrast-enhanced abdominal and pelvic CT scan is the investigational method of choice for staging and follow-up

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

- The standard treatment of localised GISTs is a complete surgical excision of the lesion, with no dissection of clinically negative lymph nodes; excision with no residual tumour at the margin (R0) is the goal
  - In low-risk GISTs located in unfavourable locations the decision can be made with the patient to accept excision with microscopic residual tumour at the margin (R1)
  - If a laparoscopic (including robotic) excision is planned, all principles of oncological surgery should be followed
  - A laparoscopic/robotic approach is clearly discouraged in patients who have large tumours, because of the risk of tumour rupture, which is associated with a very high risk of relapse
  - For selected presentations [small tumours in the upper or lower gastrointestinal (GI) tract], endoscopic excisions may be considered at sarcoma reference centres with experience in endoscopic surgery
- Adjuvant therapy with imatinib for 3 years is the standard treatment for patients with a significant risk of relapse
- An individualised shared decision-making process is needed when the risk is intermediate (i.e. in the 30-50% range)

- There is a consensus that *PDGFRA* D842V-mutated GISTs should not be treated with any adjuvant therapy, given the lack of sensitivity to imatinib of this genotype both *in vitro* and *in vivo*, and the current lack of any evidence of efficacy in the adjuvant setting for agents now available active against *PDGFRA*-mutated GIST
- In the case of *KIT* exon 9 mutation, adjuvant imatinib at a higher dose of 800 mg daily for 3 years may be considered
- There is a consensus to avoid imatinib or any adjuvant treatment in NF1-related and SDH expression-negative GISTs as well as in *BRAF*-mutated or *NTRK*-rearranged cases
- Patients at a very high risk of relapse due to tumour rupture at the time of surgery should be considered for adjuvant imatinib therapy even though the optimal duration of postoperative imatinib in this population is not defined, given the uncertainty around whether these cases should be considered as already metastatic
- If R0 surgery is not feasible, or it could be achieved through less mutilating, function-sparing surgery in the case of volumetric reduction (this includes total gastrectomy and all other major procedures), pre-treatment with imatinib is standard, as long as the mutation profile of the tumour is sensitive
  - A biopsy including mutational analysis is recommended to confirm the histological diagnosis and to exclude less sensitive or resistant genotypes to imatinib and the possible choice of an 800-mg imatinib dose for *KIT* exon 9 mutations
  - In case of *PDGFRA*-D842V mutations, the use of preoperative avapritinib may be considered
- Recommended treatment for localised GISTs with imatinib-sensitive mutations is shown in the figure on the next page

TREATMENT ALGORITHM FOR LOCALISED GISTS WITH IMATINIB-SENSITIVE MUTATIONS



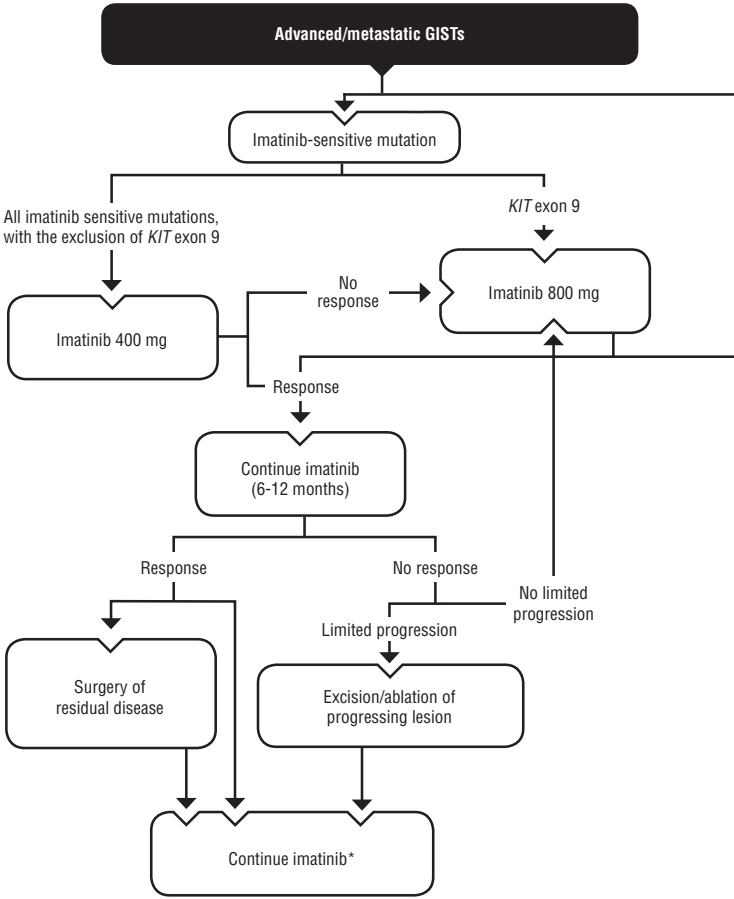
*36 months overall, considering adjuvant and neoadjuvant imatinib when preoperative imatinib is given.

GIST, gastrointestinal stromal tumour; R0, no residual tumour at the margin; R1, microscopic residual tumour at the margin.

MANAGEMENT OF ADVANCED/METASTATIC DISEASE

- Recommended treatment for advanced/metastatic GISTs is shown in the figure on the next page

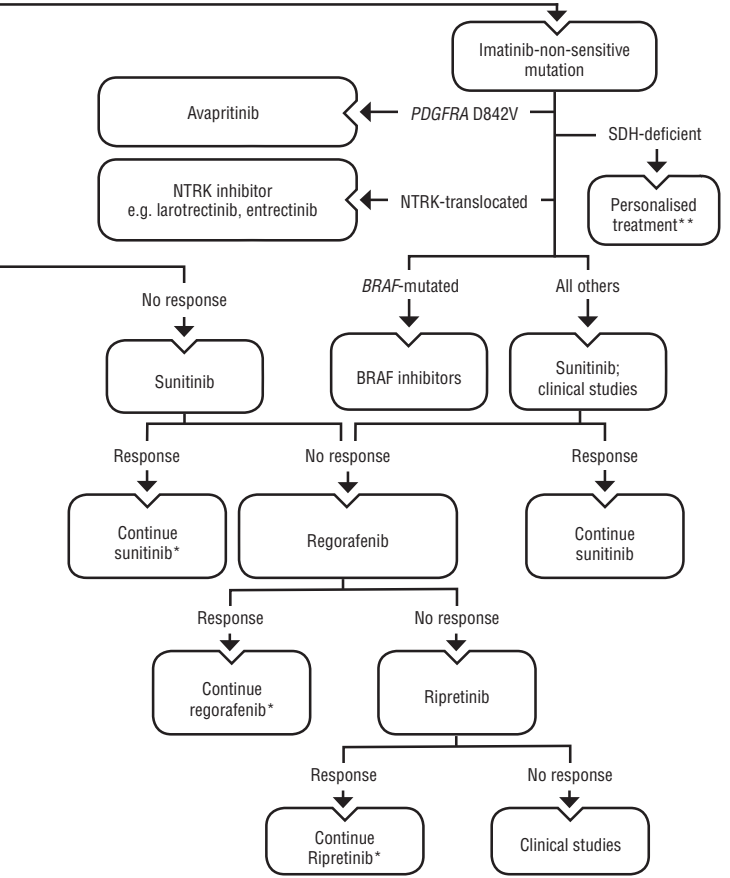
TREATMENT ALGORITHM FOR ADVANCED/METASTATIC GISTS



*Until progression.

**Refer to text of full guideline.

GIST, gastrointestinal stromal tumour; NTRK, neurotrophic tyrosine receptor kinase; SDH succinate dehydrogenase.


Imatinib-non-sensitive mutation
Avapritinib
PDGFRA D842V
SDH-deficient
NTRK inhibitor e.g. larotrectinib, entrectinib
NTRK-translocated
Personalised treatment**
No response
BRAF-mutated
All others
Sunitinib
BRAF inhibitors
Sunitinib; clinical studies
Response
No response
Response
Continue sunitinib*
Regorafenib
Continue sunitinib
Response
No response
Continue regorafenib*
Ripretinib
Response
No response
Continue Ripretinib*
Clinical studies

- Imatinib is the standard treatment for locally advanced, inoperable and metastatic patients, including patients previously treated with adjuvant imatinib who did not relapse while receiving it
- Imatinib is also the standard treatment for metastatic patients who have had all lesions removed surgically, although surgery is not recommended as a primary approach in the metastatic setting
- The standard dose of imatinib is 400 mg daily
- Standard first-line treatment for patients with *KIT* exon 9 mutations is imatinib 800 mg daily
- Standard first-line treatment for patients with *PDGFRA* exon 18 D842V mutations is avapritinib 300 mg daily
- SDH-deficient GISTs are insensitive to imatinib and can have some sensitivity to sunitinib and regorafenib
- Patients with GIST with *NTRK* rearrangement are known to have been sensitive to treatment with NTRK inhibitors such as larotrectinib and entrectinib
- GIST with *BRAF* mutations may benefit from BRAF inhibitors (including BRAF–MEK inhibitor combinations)
  - This is an off-label indication justified by biological plausibility
- In the metastatic setting, treatment with imatinib should be continued indefinitely, until clinically relevant disease progression or intolerance, because treatment interruption is generally followed by relatively rapid tumour progression, even when lesions have been previously excised surgically
  - Dose intensity should be maintained by proper management of side-effects, and a correct policy of dose reductions and interruptions should be applied in the case of excessive, persistent toxicity
- Surgery of residual metastatic disease should be individualised
- Surgical excision of progressing disease may be an option for the individual patient with limited progression, while continuing imatinib at the same dose
- In the case of tumour progression on 400 mg, an option may be to increase the imatinib dose to 800 mg daily, with the exception of insensitive mutations
- In the case of confirmed progression or rare intolerance on imatinib (after attempts to manage side-effects through expert advice, exploiting dose reductions and possibly plasma level assessment), standard second-line treatment is sunitinib 50 mg daily 4 weeks on/2 weeks off or, as an alternative schedule, 37.5 mg once daily
- Regorafenib, at the dose of 160 mg daily for 3 out of every 4 weeks, is the standard third-line therapy for patients progressing on or failing to respond to imatinib and sunitinib

- Ripretinib at the dose of 150 mg daily is the standard fourth-line treatment in patients progressing on or intolerant to imatinib, sunitinib or regorafenib
- Patients with metastatic GIST should be considered for participation in clinical trials of new therapies or combinations
- Rechallenge with imatinib (to which the patient has already been exposed) and continuation of the ongoing therapy beyond progression are options
- Radiotherapy may be considered as a palliative resource for selected patients

Response evaluation

- Response evaluation is complex, and early progression should be confirmed by an experienced team
- Both tumour size and tumour density on CT scan, or consistent changes in MRI or contrast-enhanced ultrasound, should be considered as criteria for tumour response

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

- There are no published data to indicate the optimal routine follow-up policy for surgically treated patients with localised disease
- Risk assessment based on the mitotic count, tumour size and tumour site may be useful in choosing the routine follow-up policy
- The optimal follow-up schedules are not known
  - As an example, at some institutions, high-risk patients undergo a routine follow-up with an abdominal CT scan or MRI every 3-6 months for 3 years during adjuvant therapy (with a tighter clinical follow-up due to the need to manage the side-effects of adjuvant therapy), unless contraindicated, then on cessation of adjuvant therapy every 3 months for 2 years, then every 6 months until 5 years from stopping adjuvant therapy and annually for an additional 5 years
  - For low-risk tumours, the usefulness of a routine follow-up is not known; if selected, this may be carried out with abdominal CT scan or MRI, for example, every 6-12 months for 5 years

SUMMARY RECOMMENDATIONS FOR GASTROINTESTINAL STROMAL TUMOURS

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

For patients with oesophagogastric or duodenal submucosal nodules < 2 cm, the standard approach is EUS assessment

- If biopsy is feasible and a diagnosis of GIST is made, resection should be performed, unless major morbidity is expected
- If a biopsy is not feasible or results in inadequate material for diagnosis, active surveillance is generally recommended

The standard approach to tumours ≥ 2 cm in size is biopsy/excision

Mutational analysis inclusion in the diagnostic work-up of all GISTs should be considered standard practice (with the possible exclusion of < 2 cm nonrectal GISTs).

STAGING AND RISK ASSESSMENT

The mitotic rate, tumour size and tumour site are important prognostic factors (gastric GISTs have a better prognosis than small bowel or rectal GISTs)

Tumour rupture is an additional adverse prognostic factor and should be recorded, regardless of whether it took place before or during surgery

Triple phase contrast-enhanced abdominal and pelvic CT scan is the investigational method of choice for staging and follow-up

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

The standard treatment of localised GISTs is a complete surgical excision of the lesion, with no dissection of clinically negative lymph nodes; R0 excision is the goal

- In low-risk GISTs located in unfavourable locations the decision can be made with the patient to accept possibly R1 excision
- If a laparoscopic excision is planned, the technique needs to follow the principles of oncological surgery

Adjuvant therapy with imatinib 400 mg/day for 3 years is the standard treatment for patients with a significant risk of relapse

In the case of *KIT* exon 9 mutation, adjuvant imatinib at a higher dose of 800 mg daily for 3 years may be considered

PDGFRA exon 18 D842V-mutated GISTs should not be treated with adjuvant therapy

Adjuvant treatment should be avoided in NF1-related and SDH expression-negative GISTs

Patients at a very high risk of relapse due to tumour rupture at the time of surgery should be considered for adjuvant imatinib therapy

If R0 surgery is not feasible or implies major sequelae and the tumour harbours a sensitive mutation, preoperative treatment with imatinib is standard

- In case of *PDGFRA*-D842V mutation, neoadjuvant avapritinib may be considered

MANAGEMENT OF ADVANCED/METASTATIC DISEASE

Imatinib is the standard first-line treatment for locally advanced, inoperable and metastatic patients, except for GIST without KIT/PDGFRA mutations or with a *PDGFRA* exon 18 D842V mutation

- The standard dose of imatinib is 400 mg daily

Imatinib is also the standard treatment for metastatic patients who have had all lesions removed surgically and the tumour harbours a sensitive genotype, although surgery is not recommended as a primary approach in the metastatic setting

Standard first-line treatment for patients with *KIT* exon 9 mutations is imatinib 800 mg daily

Standard first-line treatment for patients with *PDGFRA* exon 18 D842V mutations is avapritinib 300 mg daily

In the metastatic setting, treatment should be continued indefinitely, unless intolerance or specific patient request to interrupt

- Surgery of residual metastatic disease should be individualised

Surgical excision of progressing disease should be considered for an individual patient with limited progression, while continuing imatinib

In the case of tumour progression on 400 mg of imatinib, the dose can be increased to 800 mg daily (with the exception of insensitive mutations)

In the case of confirmed progression or rare intolerance on imatinib, standard second-line treatment is sunitinib 50 mg daily 4 weeks on/2 weeks off or, as an alternative schedule, 37.5 mg once daily

Regorafenib, at the dose of 160 mg daily for 3 out of every 4 weeks, is the standard third-line therapy for patients progressing on or failing to respond to imatinib and sunitinib

Ripretinib at the dose of 150 mg daily is the standard fourth-line treatment in patients progressing on or intolerant to imatinib, sunitinib or regorafenib

SDH-deficient GISTs are insensitive to imatinib and can have some sensitivity to sunitinib and regorafenib

NTRK-rearranged GISTs are known to be sensitive to treatment with NTRK inhibitors (e.g. larotrectinib, entrectinib)

BRAF-mutated GISTs benefit from BRAF inhibitors (including BRAF–MEK inhibitor combinations)

SUMMARY RECOMMENDATIONS (CONT'D)

Rechallenge with imatinib (to which the patient has already been exposed with evidence of response) or continuation of treatment beyond progression is an option

RT may be considered as a palliative resource for selected patients

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Risk assessment based on the mitotic count, tumour size and tumour site may be useful in choosing the routine follow-up policy

A policy used at some institutions is as follows:

- High-risk patients undergo a routine follow-up with an abdominal CT scan or MRI every 3-6 months for 3 years during adjuvant therapy (with a tighter clinical follow-up due to the need to manage the side-effects of adjuvant therapy), unless contraindicated, then on cessation of adjuvant therapy every 3 months for 2 years, then every 6 months until 5 years from stopping adjuvant therapy and annually for an additional 5 years

GLOSSARY

AI, anthracycline/ifosfamide
AP, alkaline phosphatase
ASPS, alveolar soft part sarcoma
ASS, adenosarcoma with sarcomatous overgrowth
BuMel, busulfan / melphalan
CCS, clear-cell sarcoma
ChT, chemotherapy
CPG, Clinical Practice Guideline
CT, computed tomography
DCS, dedifferentiated chondrosarcoma
DF, desmoid-type fibromatosis
DFSP, dermatofibrosarcoma protuberans
ESMO, European Society for Medical Oncology
ESS, endometrial stromal sarcoma
EUS, endoscopic ultrasound
FDG, [^{18F}]2-fluoro-2-deoxy-D-glucose
GCTB, giant cell tumour of bone
GI, gastrointestinal
GIST, gastrointestinal stromal tumour
HD-MTX, high-dose methotrexate
HT, hormonal therapy
ILP, isolated limb perfusion
IMRT, intensity-modulated radiotherapy
LDH, lactate dehydrogenase
LMS, leiomyosarcoma
MAP, doxorubicin/cisplatin/high-dose methotrexate
MCS, mesenchymal chondrosarcoma
MDT, multidisciplinary team
MRI, magnetic resonance imaging
MTP, muramyl tripeptide
NTRK, neurotrophic tyrosine receptor kinase
OS, overall survival
PET, positron emission tomography
R0, no residual tumour at the margin
R1, microscopic residual tumour at the margin
R2, macroscopic residual tumour at the margin
RCS, round cell sarcoma
RFA, radiofrequency ablation
RPS, retroperitoneal sarcoma
RT, radiotherapy
SFT, solitary fibrous tumour
STS, soft tissue sarcoma

UES, undifferentiated endometrial sarcoma
U-LMS, uterine leiomyosarcoma
VDC/IE, vincristine/doxorubicin/cyclophosphamide/ifosfamide/etoposide
VIDE, vincristine/ifosfamide/doxorubicin/etoposide
WB, whole-body
WHO, World Health Organization

NOTES

NOTES

Access the full ESMO Clinical Practice Guidelines

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