EUnetHTA JA3 WP4 - Other technologies, OTCA18
Review by external experts of the 1st draft Assessment report for Regional hyperthermia for high-risk soft tissue sarcoma treatment

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Jan Peter Poulsen, Oslo universitetssykehus	General		The report is very thoroughly done. I am impressed by the work the authors have done. It gave me a great pleasure to read. According to my point of view, it could not have been better.		Thank you
Frank Lohr, University of Modena, Italy	General		Very readable report		Thank you
			- the issue of acute vs. late side effects has been discussed in depths, the solution that you chose is acceptable for me		Ok
			- if you agree with my interpretation of the issue of the difference in PFS between the first and the second publication of the EORTC trial (simple typo/data insertion error in the table) the Results/Discussion/Conclusion section should be changed accordingly.		This issue is clear now. The difference can be explained by the fact that the 2010 data are intermediate and the median was not yet reached.
Stephan Bodis, Kantonsspital Aarau, University Hospital and University of Zurich, Switzerland			Overall thorough and complete assessments based on few clinical data (but that how it is)		Thank you

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	14		Add ESMO definition of high risk sarcoma (from page 69)	2	Ok
	35		Oncotherm – selective focus on tumor cells This is highly controversial. The report should declare more prominently that all this information were taken form the website and do not reflect the opnion of the authors of this report	1	Thank you. We agree that claim may not be adequately supported although – for the same reason - we would prefer not to refer on our opinions. In this context, we highlighted that the information presented and related claims are those available on the website of the producer, using the conditional tense to describe potential effects claimed by the producer
Toto Hølmebakk, The Sarcoma Group, Department of Abdominal Surgery, Oslo University Hospital	General		It should be specified throughout the document whether the text applies to soft tissue sarcoma (STS) in general, to STS of the extremities and trunk, of the abdomen, retroperitoneum or head and neck. STS in these various locations differ in treatment and prognosis.	1	Thank you for the comment. In the first draft we specified that we include STS arising from all of these locations in the SCOPE (See chapter 1.1. page 13second paragraph under description of Population in the scope). In the second draft we include the statement also in the CUR chapter 4.2)
	General		Gastrointestinal stromal tumour (GIST) is the most common sarcoma (20 per cent). It should be made explicit at the beginning of the document and throughout whether this entity is excluded. GIST is not classified or graded	1	Thank you for your comment. We totally agree and we better specified it in the chapter 4.2 of the CUR

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			as other STSs, surgical considerations are not the same, and most importantly, oncological treatment is quite different.		domain "Description of sarcoma and subtypes" paragraph). We added a sentence in the ICD-O-3 codes list in order to exclude GIST. .
	General		It is stated, in different sections of the document, that there are 50, 70 and more than a hundred different subtypes of STS. This inconsistency should be corrected.		Thank you, corrected considering more than a hundred different subtypes of STS.
	General		There is inconsistent use of British and American spelling, e.g. tumour/tumor; -ised/-ized etc.	3	This will be corrected in the prefinal version.
	29		It should be stated explicitly that surgery is not only 'the mainstay' of treatment, but a prerequisite for cure for most types of STS.	2	Thank you. Done.
	29		Decisions on surgery are also based on histological type, and, importantly, on the patient's age and general medical condition.	1	Thank you. We added this criteria to the sentence.
	30, 1st paragraph		The text refers to the Enneking classification. This system is applicable essentially to STSs of the extremity and trunk wall. For STS in other locations, the R classification applies. These systems are not compatible/interchangeable, e.g. a marginal excision according to the Enneking system may be either a R0 or an R1 resection; and an intralesional excision may be either a R1 or an R2 resection. The R classification is increasingly used also for STS of the extremities. The systems should be described more in detail and the differences between them discussed. The original references should be given: Enneking 1980,	1	Thank you. We described these two systems more in detail and added the references you suggested

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			Clin Orthop Relat Res; and Wittekind 2002, Cancer.		
	30/31		Targeted therapies should not be classified among chemotherapeutic agents. Targeted therapies deserve a separate paragraph, especially if GIST is included among the STSs. Chemotherapy is probably too superficially described.	2	Thank you for your comment. We separate the short paragraph on targeted therapies from the one on chemotherapy. Since targeted therapy is not a comparator in our assessment and GIST are not included, we think that a brief reference is sufficient. In the first draft we also tried to report the most important features on chemotherapy use without going in a too deep discussion, as not the main focus of this HTA.
	31		I think a paragraph on isolated limb perfusion (ILP) would be appropriate.	2	Thank you. We added some text about ILP in the Regional hyperthermia for Soft 1 Tissue Sarcoma paragraph
	58	19	GIST should be mentioned as it is the most common STS.	1	Thank you. Done.
	58	26	Well differentiated liposarcoma has no metastatic potential	2	Ok, corrected, thank you.
	60		Table 4.1 is misleading as it gives the impression that many STSs have known aetiologies. Most STSs are sporadic, and hereditary or environmental factors play a role only in a minority of cases; e.g. familial GIST comprises less than one per cent of cases. If the table is retained, the	1	Thank you for your comment. The concept you are highlighting is reported in the first draft just above the Table 4.1. We added a sentence to stress it more. We think that giving

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			proportion of cases that can be ascribed to these factors should be stated.		precise % is misleading, due to paucity of data and the methodological issues in the association between STS and each risk factor.
	61		Cf. comment above. The impact of hereditary and environmental factors should be specified (per cent) as their importance is insignificant in most STSs.	2	See answer to the comment above.
	61	48	A better example of an indolent STS would probably be well differentiated liposarcoma.		Thank you. Added.
	62		Pattern of spread: It should be mentioned, if the document does not exclude GIST altogether, that GIST metastasizes to the liver and peritoneum, hardly ever to the lungs.	2	Thank you for the comment. As previously stated we do not include GIST in this assessment.
	63	5-8	Clinical presentation: GIST, the most common sarcoma (20 per cent), should be mentioned.	1	Thank you for the comment. As previously stated we do not include GIST in this assessment.
	67	10-13	For retroperitoneal and abdominal sarcomas, CT (not MRI), is mandatory.		Thank you. Added.
	67	16	Open biopsy is discouraged, and if necessary, it should be performed in a sarcoma centre.	2	Thank you. Added.
	67	18	There are lot of other information that should be included in the pathology report, and I would suggest that this document just stated that the pathological examination should be done by a sarcoma pathologist.	1	Thank you. We agree. Added.
	67	26	For sarcoma, the TNM classification does not apply well and is not in	1	Thank you. We expanded that

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			clinical use. This reference should be deleted.		paragraph to try to put the TNM classification system more in the context of its use and of other available systems.
	68		There are two widely used nomograms for GIST: Gold (Lancet Oncol 2009) and Joensuu (Lancet Oncol 2012).	2	Thank you for the comment. As previously stated we do not include GIST in this assessment.
	68		The Sarculator should be mentioned in this paragraph.	2	Thank you. Added
	69	11	It should be stated explicitly that for retroperitoneal sarcoma, neo- or adjuvant treatment is without documented benefit (The STRASS trial, Abstract ASCO 2019).	1	Thank you. Added
	70	3	As for adjuvant therapy, the SSG XX trial should be referred to (Sundby Hall, Eur J Cancer 2018) as well as the ISG-STS 1001 trial (Gronchi, Lancet Oncol 2017). These trials show a decisive effect of adjuvant therapy for high-risk STS compared to historical series – probably the best evidence there is for adjuvant treatment.	1	Thank you. According to their objectives and results, we added these references in the adjuvant (Sundby) and neoadjuvant (Gronchi) paragraphs, respectively.
	70	13	Adjustments have to be made for histotype and location. For retroperitoneal sarcoma, postoperative treatment has no documented effect; for dedifferentiated liposarcoma, chemotherapy is rarely effective.	2	Thank you for your comment. We need references to support your statements in this regard. What we report here is an overview of ESMO recommendations.
	70	32	This is not correct. Response rates are superior with combination therapy; survival, however, is not.	1	As reported in the previous comment, we need references to support this statement. We reported

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					reccomendations from ESMO guidelines.
	70	39	'…with lung metastases' should be deleted, as STSs metastasizes to other organs as well.		We agree and we changed "lung" with "distant".
	72	19	Anatomical location should be added: e.g. RP sarcoma and sarcomas of the head and neck have a worse prognosis than STS of the extremities	2	Thank you. Added.
	72	20	As noted above, the TNM classification is not well adopted to sarcoma. Reference should be done to other publications for assessment of prognosis.	1	Here we do not endorse the TNM classification but just report available five-year rates disease-free survival for stage I, II, and III disease (from a study adopting the TNM classification)
	72	25	Earlier in the document it is said that 10 per cent of STS are metastatic at diagnosis. A definition of 'locally advanced' should be given in order to explain the discrepancy.	1	Thank you for your comment. We rephrased the sentence to solve the discrepancy.
	72	37	As commented above, this is not correct. Response rates are higher with doxorubicine/ifosfamide than doxorubicine alone but survival is not improved with combination therapy.	1	As reported above, we need references to support this statement.

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