Managing Extremity Soft Tissue Sarcoma Patients: Surgery Alone or in Combination with Radiotherapy? An Editorial on the Paper by Fiore et al

Haas, R.

Managing extremity soft tissue sarcoma patients; surgery alone or in combination with radiotherapy?

An Editorial on ASO-2017-11-2061

Dr Fiore and colleagues are to be congratulated on their analysis on local control probability after surgery alone in high risk extremity soft tissue sarcomas (ESTS). Although both NCCN- [1] and ESMO- [2] guidelines suggest to combine limb salvage surgery with radiotherapy (RT) and although currently there are no data available from randomized studies suggesting to refrain from RT, Dr Fiore's results are remarkable in several ways, but also need to be considered in the right perspective.

What are the remarkable findings?

There were less R0 resections, 69.4% versus 78.9% (p=0.182), in patients in group B (without RT) as compared to those in group A. Yet, local control in both groups was comparable. What one would expect, is that specifically in a subgroup with R1 resections, perioperative RT would compensate for these microscopically positive margins with respect to local control, which it did not; 66.3% versus 72.1%.

The local failure rate without RT in R1 resections in this manuscript is 27.9%. As found by Alektiar, (manuscript reference #24), and many others, radiation would decrease the local failure rate with a factor of 2 to 3, mounting to a failure rate of 9-14% and so a local control estimate of 86-91%. This rate is comparable to the literature. However, in Dr Fiore's manuscript it is unexpectedly lower at 66.3%.

The local failure rate without RT in R0 resections in this manuscript is fairly low at 14.8%. If again the risk on local relapse would be reduced with a factor of 2 to 3, a local failure rate of 5-8% would be expected leading to a local control estimate of 92-95%; in their series it was 88%. Also these rates are comparable to the literature, specifically to the data obtained by O'Sullivan in the Canadian randomized SR-2 trial [3]. What remains unexplained (except for selection biases on histology and the performance of isolated limb perfusions) is the observation that in their setting, the addition of RT to limb sparing surgery led to so little gain in local control and this is contradictory to many other series [3, 4]. Furthermore, the definition of resection margins may differ across institutes. Very recently, Gundle et al proposed a clinically meaningful classification system that may serve as a standardization method [5]. Another issue to consider more in-depth, is the timing of RT. The data are reported in the manuscript and for overview have been summarized in the table below. RT was administered predominantly postoperatively RT, and as such RT did not increase local control as compared to surgery alone. However, when performed preoperatively, local control rate increased by an absolute gain of 3.9% (in case of R1) to 7.8% (in case of R0).

A reasonable interpretation of these data with respect to surgery alone in high risk ESTS could be that referral to highly experienced sarcoma surgeons translates into high local control rates even when selectively (not routinely) refraining from perioperative RT. This observation has also been reported by Blay et al [6] suggesting significantly more R0 and less R2 resection, less reoperations and a higher relapse free survival and local relapse free survival in reference centers.

Studying wound complications is yet another elaboration on surgical skills and the obvious need to have sarcoma patients treated at reference centers. Several series suggest a wound complication rate after surgery alone of about 17%, but a doubling to 35% if surgery was preceded by preoperative RT [3, 7]. Although the specific criteria for registering a wound complication are not described, Dr Fiore and co-workers recorded a substantially lower rate of 13.6% overall. Somewhat surprising is that this rate was 20.5% in the group without radiotherapy and 11.9% in the group with perioperative radiation, which one would have expected to be the other way around. This paradox, however, can be explained by the selection biases of patient not undergoing radiotherapy as described in Table 2. Roughly two-thirds of the reasons not to apply radiation had to do with (the anticipation of) complications and therefore the radiation abstention was an individualized approach [8].

The take home messages from this important manuscript could be:

- Referral to experienced sarcoma surgeons may lead to higher local control rates after limb sparing surgery alone than would be expected from other reports (this study and [5]).
- Referral to experienced sarcoma surgeons may lead to lower wound complication rates (this study and [3]).
- When RT is offered, the absolute gain in local control may be higher after preoperative RT as compared to postoperative RT, irrespective of resection margin status (this study and [9])
- Obviously, the addition of RT to increase local control rates as compared to surgery alone, comes at the cost of a toxicity profile that differs between pre- (wound complications) and postoperative RT (permanent late functional deficits) [3, 10]. The decision on prescribing RT should not be taken lightly and best left to experienced multidisciplinary teams. Having stated that, until well designed randomized studies on the additional value of RT as well as RT-dose so dictate (e.g. NCT00870701, NCT02565498), standard management of high risk ESTS remains a combination of limb sparing surgery and RT [1, 2].

References

1 von Mehren M, Randall RL, Benjamin RS, et al. National Comprehensive Cancer Network. Soft tissue sarcoma, version 2.2016. J Natl Compr Canc Netw. 2016;14:758-86.

2 The ESMO/European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25:iii102-112.

3 O'Sullivan B, Davis AM, Turcotte R et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet. 2002;359:2235-41.

4 Beane JD, Yang JC, White D et al. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. Ann Surg Oncol. 2014;21:2484-9.

5 Gundle KR, Kafchinski L, Gupta S et al. Analysis of Margin Classification Systems for Assessing the Risk of Local Recurrence After Soft Tissue Sarcoma Resection. J Clin Oncol. 2018 Jan 18:JCO2017746941. doi: 10.1200/JCO.2017.74.6941. [Epub ahead of print]

6 Blay JY, Soibinet P, Penel N et al. Improved survival using specialized multidisciplinary board in sarcoma patients. Ann Oncol. 2017;28:2852-2859.

7 Cannon CP, Ballo MT, Zagars GK et al. Complications of combined modality treatment of primary lower extremity soft-tissue sarcomas. Cancer. 2006;107:2455-61.

8 Gronchi A. Individualizing the use/non-use of radiation therapy (RT) in soft tissue sarcoma (STS): When abstention is better than care. J Surg Oncol. 2015;111:133-4.

9 Sampath S, Schultheiss TE, Hitchcock YJ et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma: multi-institutional analysis of 821 patients. Int J Radiat Oncol Biol Phys. 2011;81:498-505.

10 Davis AM, O'Sullivan B, Turcotte R et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol. 2005;75:48-53.

Local control rates in different subgroups in ASO-2017-11-2061

	no RT, group B	with RT, Group A					
		All perioperative RT		Preoperative RT		Postoperative RT	
	n=72	n=318	P value	n=107	Absolute gain	n=211	Absolute gain
R0	**85.2%** (n=50)	**88%** (n=251)	0.240	**93%**	+7.8%	87%	+1.8%
R1	**72.1%** (n=22)	**66.3%** (n=66)	0.730	**76%**	+3.9%	66%	-6.1%

Abbreviations:
RT = radiotherapy, n = number.
Note for group A: 251+66=317, there was 1 other case with an R2 resection