

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

Rick Haas, MD, PhD<sup>1,2</sup>

<sup>1</sup>Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands; <sup>2</sup>Department of Radiotherapy, Leiden University Medical Center, Leiden, The Netherlands

Dr Fiore and colleagues are to be congratulated on their analysis of local control probability after surgery alone in high-risk extremity soft tissue sarcomas (ESTSs).<sup>1</sup> Although both national comprehensive cancer network (NCCN)<sup>2</sup> and European society for medical oncology (ESMO)<sup>3</sup> guidelines suggest combining limb salvage surgery with radiotherapy (RT), and although no data are currently available from randomized studies suggesting to refrain from RT, the results from the study by Dr Fiore et al. 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% vs. 78.9%;  $p = 0.182$ ) in patients in group B (without RT) compared with 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% vs. 72.1%.

The local failure rate without RT in R1 resections was 27.9%. As found by Alektiar (manuscript reference #24) and many others, radiation would decrease the local failure rate with a factor of 2–3, mounting to a failure rate of 9–14%, and therefore a local control estimate of 86–91%.

This rate is comparable with the literature; however, in the study by Fiore et al., it is unexpectedly lower at 66.3%.

The local failure rate without RT in R0 resections was fairly low at 14.8%. If, again, the risk on local relapse was reduced with a factor of 2–3, a local failure rate of 5–8% would be expected, leading to a local control estimate of 92–95%; in the study by Fiore et al. the rate was 88%. In addition, these rates are comparable with the literature, specifically pertaining to the data obtained by O’Sullivan et al. in the Canadian randomized SR-2 trial.<sup>4</sup> 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, which is contradictory to many other series.<sup>4,5</sup> Furthermore, the definition of resection margins may differ across institutes. Gundle et al. recently proposed a clinically meaningful classification system that may serve as a standardization method.<sup>6</sup> Another issue to consider more in-depth is the timing of RT. The data are reported by Fiore et al., and, for overview, have been summarized in Table 1 below. RT was predominantly administered postoperatively, and as such it did not increase local control compared with surgery alone. However, when performed preoperatively, the local control rate increased by an absolute gain of 3.9% (in cases of R1) to 7.8% (in cases of R0).

A reasonable interpretation of these data with respect to surgery alone in high-risk ESTSs 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.<sup>7</sup> suggesting significantly more R0 and less R2 resections, less reoperations, and higher

**TABLE 1** Local control rates in different subgroups in the Fiore et al. study

	No RT, group B [n = 72]	With RT, group A		Preoperative RT		Postoperative RT	
		All perioperative RT [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%

Note for group A: 251 + 66 = 317, there was one other case with an R2 resection  
RT radiotherapy

relapse-free survival (RFS) and local RFS 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 approximately 17%, but a doubling to 35% if surgery was preceded by preoperative RT.<sup>4,8</sup> 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 RT and 11.9% in the group with perioperative radiation, which one would have expected to be the other way around. However, this paradox can be explained by the selection biases of patients not undergoing RT, as described in Table 2 of the Fiore et al. study. Approximately 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.<sup>9</sup>

The take home messages from this important article by Fiore et al. could be as follows.

- Referral to experienced sarcoma surgeons may lead to higher local control rates after limb-sparing surgery alone than would be expected from other reports (see the studies by Fiore et al. and Gundle et al.<sup>6</sup>).
- Referral to experienced sarcoma surgeons may lead to lower wound complication rates (see the studies by Fiore et al. and O'Sullivan et al.<sup>4</sup>).
- When RT is offered, the absolute gain in local control may be higher after preoperative RT compared with postoperative RT, irrespective of resection margin status (see the studies by Fiore et al. and Sampath et al.<sup>10</sup>).
- Obviously, the addition of RT to increase local control rates compared with surgery alone comes at the cost of a toxicity profile that differs between preoperative (wound complications) and postoperative RT (permanent late functional deficits).<sup>4,11</sup> The decision on prescribing RT should not be taken lightly and is 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 ESTSs remains a combination of limb-sparing surgery and RT.<sup>2,3</sup>

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