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Platinum Priority – Editorial

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The Finnish Randomized Trial of Adjuvant Radiotherapy Versus Observation After Prostatectomy: Almost a Trial of Adjuvant Versus Late Salvage Radiotherapy

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As has been demonstrated now in four randomized trials discussed here, a substantial number of men with adverse pathology, even with clinically low- or intermediate-risk disease, will experience biochemical recurrence (BCR) of their prostate cancer (PC) after radical prostatectomy (RP) [1–3]. The high recurrence rates after RP prompted the investigation of adjuvant radiotherapy (ART) as a potential therapeutic strategy for this population of men more than three decades ago.

1. From three to now four ART trials

In this issue of *European Urology*, Hackman and colleagues [4] report on the Finnish randomized trial, which is now the fourth trial to investigate the benefit of ART after RP. This trial has numerous strengths. The follow-up was mature at 9 yr, similar to the EORTC and German trials [1,3]. It is substantially more contemporary and enrolled patients during 2004–2012, in contrast to 1988–2004. Other than the EORTC trial, it is the only trial to specifically report results for patients with pT2 disease and positive surgical margin (PSM) in the trial, and greatly expands our understanding of the benefit of ART for this patient population [1]. It also specifically excluded patients with seminal vesicle invasion (SVI), who have a very high chance of recurrence after RP [2]. The RT dose used (66.6 Gy) was higher than in the other three trials (60 Gy) and three-dimensional conformal RT was used instead of the two-dimensional RT used in the SWOG and EORTC trials [1,2]. The Finnish trial also importantly collected data on both physician-reported toxicity and patient-reported quality of life.

The weaknesses are well stated by the authors: the sample size is small and thus is not sufficiently powered to detect differences in metastases or OS, even if any exist. Although not necessarily a limitation, approximately 50% of the men in both arms of the trial had detectable prostate-specific antigen (PSA) at trial entry of 0.2–0.5 ng/ml, so this was not a true adjuvant trial among patients with undetectable PSA (in contrast to the German trial, in which all patients had PSA $<$ 0.2 ng/ml on entry) [3].

2. Key results of the Finnish trial

The primary endpoint of the Finnish trial, like the EORTC and German trials [1,3] was BCR, which was improved with ART (hazard ratio [HR] 0.26; absolute improvement of 21% at 10 yr). In a meta-analysis of the three original ART trials, the pooled HR estimate was 0.48 for a BCR benefit with ART [5]. Thus, it is probable that the greatest relative benefit was seen for patients treated in the Finnish trial. This may be because patients with pT2 disease with PSM derived the greatest benefit from ART (BCR: 4% vs 33% for pT2 with PSM compared to 22% vs 37% for pT3a disease in the ART vs observation arms, respectively). Although not statistically significant, the point estimate for both metastasis-free survival (MFS; HR 0.49) and castration-resistant PC (CRPC)–free survival (HR 0.50) favored the ART arm.

Importantly, ART was associated with higher moderate to severe toxicity. The Finnish trial demonstrated an 8% higher

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crude rate of grade ≥3 genitourinary toxicity, no difference in severe gastrointestinal toxicity, and higher rates of erectile dysfunction in the ART arm. This is in contrast to the EORTC trial, in which ART led to only a 2% increase in grade ≥3 toxicity, and the German trial in which ART led to a 3% increase in grade ≥3 genitourinary toxicity and no increase in severe gastrointestinal toxicity [6]. Thus, ART reduced BCR at the expense of an increase in severe toxicity, something well established from previously reported trials.

3. Realistic estimates of recurrence and toxicity after RP

The Finnish trial transparently demonstrated that even in this population with clinically low and intermediate risk disease, 40% of patients who are observed after RP will develop BCR (defined as PSA of 0.4 ng/ml). Furthermore, RP alone was associated with very high rates of moderate and severe toxicity. In fact, 87% of RP-alone patients experienced a grade 2 and 40% a grade 3 adverse event. Patients should be counseled regarding these high rates of recurrence and toxicity when deciding on their local treatment approach.

4. Perhaps the most unique (and important) aspect of the Finnish trial

Of patients who developed BCR in the observation arm of the Finnish trial, salvage RT (SRT) was used in 86% of patients at median PSA of 0.7 ng/ml, and 75% of these patients had no evidence of disease at time of last follow-up. Thus, SRT is highly effective, which is why it is the guideline-concordant standard of care for men who experience BCR after RP [7]. By contrast, one of the primary criticisms of the SWOG and EORTC trials was that SRT was used in only ~30% of patients in the observation arm at relatively high PSAs of 1.0 and 1.7 ng/ml, respectively [6]. It is well established that the lower the PSA on receipt of SRT, the more likely it is that patients will be cured of their disease [8].

Thus, in essence the Finnish study is almost a trial of ART versus late SRT. In this context, late SRT had lower toxicity, better quality of life, and small absolute differences in subsequent disease progression (eg, developing metastatic disease or CRPC). Although not statistically different, it is concerning that there is a signal that development of metastatic disease may be higher in the observation arm (2% absolute), especially in this cohort with relatively favorable risk, and longer follow-up may make these differences more pronounced. In addition, if this was a higher-risk population that included higher-grade disease, SVI, or a significant proportion of Decipher high-risk tumors, a HR of 0.49 could translate into a much larger absolute difference in MFS. However, we already know that early SRT is substantially more effective than late SRT, and thus in the pending trials comparing ART versus early SRT it is improbable that any difference in the development of metastatic disease will be detected among genomically unselected patients given that all patients will receive SRT (in contrast to 86%) and all will receive early SRT (in contrast to late SRT).

5. Importance of SRT: lessons from the Finnish trial

The signal of a higher rate of metastatic events in the observation arm is of potential concern, not in this trial, but in the real world. This is because recent data from the USA demonstrate that although guidelines recommend giving SRT early at the time of BCR, only 30% of patients who experience BCR receive any SRT (similar to SRT rates in the SWOG trial) [9]. This is far lower than the 86% SRT utilization rate seen in the Finnish trial. Thus, there is already a small signal in the Finnish trial that more metastatic events are developing in a cohort that nearly uniformly received SRT. If patients are not referred for SRT in routine practice, especially early SRT, it is probable that those who initially undergo observation after RP will have worse long-term outcomes than those receiving upfront ART, and the results of the SWOG trial demonstrating improvements in MFS may in fact be applicable.

In conclusion, the Finnish trial in my eyes further supports the use of observation as an approach after RP, but only if SRT, especially early SRT, utilization rates are very high. Furthermore, given the favorable-risk nature of the Finnish trial, it is unclear whether patients with SVI or Decipher high-risk disease would have similar results given their substantially higher rate of recurrence [10].

Conflicts of interest: The author has no conflicts of interest relevant to this manuscript. He participates in advisory boards for Janssen and Blue Earth.

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