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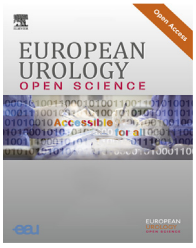

European Association of Urology

Open to Debate – Referee

Stage II Seminoma: Is There Something New on the Horizon?

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Seminomas are radiosensitive tumors for which radiotherapy (RT) has historically been the standard of care (SoC) in stage II A/B disease, with relapse rates between 9% and 24% reported [1,2]. Despite its efficacy, chemotherapy has overtaken its role due to concerns about long-term radiation-induced non-germ cell malignancies [3,4]. RT and chemotherapy show similar efficacy, but higher long-term toxicity has been reported for RT [5]. On this basis, the European Association of Urology guidelines suggest reserving RT for patients who are unfit for chemotherapy. However, one must remember that this change in management is based solely on observational data. With observations on the long-term toxicity of RT, it makes sense that chemotherapy became the SoC. However, more recently it has become clear that chemotherapy also has long-term side effects. Among long-term survivors, chemotherapy is associated with secondary cancers (mainly leukemia, and solid tumors to a lesser extent) and lower overall survival at long-term follow-up [6,7]. Furthermore, well-known and irreversible neurotoxicity and ototoxicity in up to 16% of long-term survivors [8] and bleomycin-induced pulmonary toxicity can lead to restrictive lung disease in up to 17% of cases on long-term follow-up [9]. Finally, chemotherapy has been associated with long-term hypogonadism and cardiovascular disease [10,11]. These observations are reflected in the National Comprehensive Cancer Network guidelines, which recommend chemotherapy and RT as equivalent treatment options. Furthermore, the guidelines note that novel RT regimens retain efficacy while potentially reducing side effects [1]. No one will dispute that both treatments are effective. However, in the absence of any comparative data, there is significant uncertainty regarding the rate of overtreatment of stage IIA/B seminoma of the testis. Most will also agree that we must strive towards treatment de-escalation with the goal of reducing associated toxicity while maintaining treatment efficacy.

In this Open to Debate series, Naoun et al. [12] argue that the future is individualized de-escalation of chemotherapy regimens, highlighting the SEMITEP and SAKK 01/10 trials [13,14]. The SEMITEP trial suffers from some methodological issues that prevent routine use of this regimen. First, the primary outcome of this study is a metabolic response according to fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) negativity at interim analysis after two cycles of etoposide and cisplatin (EP). The issue with this approach is that the specificity of FDG PET/CT is limited, with false-positive findings in up to 64% of cases [15]. Second, in a trial aiming for treatment de-escalation, there is no solid biological explanation given for the "backup" treatment of an additional cycle of carboplatin for responders to two cycles of EP [16]. Lastly, the SEMITEP trial included both stage IIC–III and stage IIA–B disease. However, for the latter an alternative curative treatment option already exists: dog-leg RT, which is where the SAKK 01/10 study comes into play. The aim of SAKK 01/10 was to exploit a potential synergistic effect of chemotherapy and RT and reduce the treatment intensity of both modalities. The first results from this study look promising, as acute toxicity was lower for this combination in comparison to

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historical cohorts [14]. Owing to the limited follow-up, uncertainty remains regarding the long-term toxicity and secondary malignancies. However, as it takes more than 10 yr to develop therapy-related secondary malignancies, it is unrealistic to wait for these observations before changing treatment recommendations. If efficacy has been shown and it is expected that a certain treatment is less toxic than the current SoC, a novel SoC could be considered. In this regard, results are eagerly awaited from the upcoming SAKK 01/18 trial, in which a further RT dose reduction of 20% is being used (to further reduce toxicity) in combination with one cycle of EP instead of carboplatin (to target micrometastatic disease; NCT03937843).

Another approach to de-escalate treatment and avoid treatment-related toxicity is primary retroperitoneal lymph node dissection (RPLND), which is an attractive approach because it avoids RT- and chemotherapy-related toxicity in most patients. As stated by Alsyouf and Daneshmand [17], novel surgical approaches have minimized hospital stays and postoperative complication rates and are associated with limited long-term toxicity [18]. For all ongoing trials that have reported preliminary data (SEMS, COTRIMS), recurrence rates range between 9.5% and 29% at 2-yr follow-up, so 71–91.5% of patients can avoid any additional treatment. As most recurrences occur within 3 yr after RT and chemotherapy [13,19], outcomes reported for these studies still lack sufficient follow-up to draw definitive conclusions regarding long-term recurrence rates. The recently published PRIMETEST trial did not reach its primary endpoint; the trial would have been considered positive if <30% of patients experienced recurrence after 3 yr. However, the results were published before the 3-yr follow-up mark because recurrence rates were higher than expected, with recurrence-free survival of 70% (95% confidence interval 51–84%) at median follow-up of 32 mo [20]. Although the primary endpoint was not met, there are some very interesting observations in this study. First, surgical treatment seemed safe, with a limited number of Clavien-Dindo grade $\geq$3 complications. Second, 9% of the patients had negative final histopathology. This implies that a significant proportion of patients would have been subjected to the long-term toxicity of the current SoC without gaining any benefit. In total, the treatment burden of chemotherapy was reduced in 23/33 patients in this trial, which is far from insignificant. Finally, although the follow-up is limited, all patients are in remission after salvage chemotherapy. This is why we believe that future trials should not investigate progression-free survival as the primary endpoint. In a few years and with the upcoming full publications of the SEMS and COTRIMS trials, we will have a good insight into recurrence rates after surgical treatment. Future trials should focus on the oncological safety of postponing salvage therapies after primary RPLND (remission-free survival after salvage therapies). Even if a significant proportion of patients experience recurrence after primary RPLND, if they can be safely treated with salvage therapies, the treatment burden with chemotherapy and/or RT would still be significantly reduced.

In conclusion, both sides of the debate agree that current long-term treatment-related toxicities are no longer acceptable. Although the current evidence is too immature to set a new SoC, the treatment of stage IIA/B seminoma is very likely to drastically change in the future. We believe that both primary RPLND and/or a form of de-escalated chemo (radio)therapy will play a role. Treatment strategies will probably become more diverse and will hopefully result in more individualized regimens. Future trials will show which patients are best suited for surgery, chemotherapy, or RT on the basis of both clinical factors and biomarker studies.

Conflicts of interest: The authors have nothing to disclose.

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