Title Page

Title of the article: READRESSING THE RATIONALE OF IRRADIATION IN STAGE I SEMINOMA GUIDELINES: A CRITICAL ESSAY.

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Introduction

Germ cell tumors (GCT), accounting for 95% of malignant testicular tumors (1), can be divided into two groups: seminoma (SGCT) and non-seminoma (NSGCT). Seminomas typically arise in men in the fourth decade of life, compromising 60% of the GCT (2). At diagnosis, approximately 75% present with local disease (Stage I); 15% is detected with metastatic regional lymph nodes (Stage II) and 5-10% present with juxtaregional or visceral metastasis (Stage III) (3) .

In stage I, inguinal orchiectomy is used both for diagnosis and treatment purpose (4). Until a decade ago, three adjuvant management options were available in stage I SGCT: radiotherapy, chemotherapy and active surveillance.

Currently, active surveillance (AS) is well-established as the management of choice as 85% of patients with stage I seminomas are cured after orchiectomy alone (4-7). Any adjuvant therapy may result in a substantial number of overtreatment and the exposure of a patient to the associated risk of adverse effects (8). In well-organized AS protocols, all relapses occurred within the first three years, with 17% relapsing in year three (6).

On the other hand, in patients presenting with adverse prognostic features at the orchiectomy specimen, up to 32% recur after 10 years (9). Risk stratification is commonly based on tumor diameter and rete testis invasion (RTI) (10, 11), thereby tumor size seems to be linearly correlated with the risk of recurrence with a most often used cut-off of 4 cm. It was the only of the two risk factors in the prognostic model published by Warde (12) that could be

1 validated (8), corresponding to other retrospective findings (13). Prospective data (10,11)
2 however have confirmed the association of both risk factors with the risk of recurrence.
3 Although salvage treatments result in excellent survival outcomes, this comes at the cost of
4 treatment-induced toxicity as salvage therapy is more aggressive (9). Therefore, in high-risk
5 patients, adjuvant treatment with chemotherapy or radiotherapy (RT) is considered (12)
6 although the use of RT has been heavily criticized. While the current NCCN and to a lesser
7 extent, the ESMO guidelines (14, 15) include RT as a valid adjuvant treatment option, the
8 guidelines of the European Association of Urology (EAU) removed adjuvant RT as a
9 treatment choice and only kept carboplatin area under the dose-time concentration curve
10 (AUC) 7 as active adjuvant treatment (16). Presumably, this decision was based on the
11 hypothesis that adjuvant RT induces more secondary malignancies (SMN) compared to
12 carboplatin AUC 7. This assumption arose from the MRC TE 19 trial published by Oliver et
13 al. who reported on the non-inferiority of carboplatin AUC 7 (one cycle) compared to RT (17)
14 while RT induced more SMN. Although the latter has been contested by others (7,9), the
15 controversy has never been reflected in the EAU guidelines for testicular cancer, endorsed by
16 more than 40 countries worldwide (18). Consequently, the use of radiotherapy has
17 dramatically declined over the past decade (19). This comment critically analyses some
18 assumptions derived from the MRC TE 19 trial (17) and provides evidence that the
19 radiotherapy schedule and technology used in this paper need to be revisited in view of more
20 advanced RT techniques.

21
22 Is adjuvant Carboplatin (1 cycle) really non-inferior to radiotherapy?

23
24 Adjuvant treatment with RT after orchiectomy has been the standard treatment for stage I
25 seminoma for decades. Due to its high radiosensitivity and predictable pattern of spread to the
26 para-aortic lymph nodes as a first echelon, adjuvant RT results in long-term relapse-free and
27 cancer-specific survival rates as high as 95% and 98% respectively (20). The 15-20% risk of
28 relapse after surveillance alone decreases to three to 5 % after adjuvant RT (12,21).

29 In order to demonstrate that the novel treatment with single agent carboplatin AUC 7 is not
30 less effective than comparator radiotherapy, defined by a pre-specified non-inferiority margin,
31 Oliver et al. performed the MRC TE19 randomized non-inferiority trial (17). Radiotherapy
32 consisted of a dog-leg field (DL) in 13% and para-aortic strip (PA) in 87% of the cases. RT
33 dose of 20 Gy was given in 36%, 30 Gy in 54% and an in-between dose in 9 % of the
34 patients. The primary endpoint was relapse-free rate (RFR) and the trial was designed to

1 exclude a 3 % absolute difference in two-year rates with a 90% certainty (one-sided). In the
2 first publication (2005), the conclusion of this trial was that one cycle of carboplatin AUC 7
3 was non-inferior to adjuvant RT hereby excluding a difference in RFR >3%. However, in the
4 updated publication with a median follow-up of six and a half years (22), the five-year RFR
5 after RT was 96.0% (CI: 94.5%-97.1%) compared to 94.7% (CI: 92.5%-96.3%) after
6 carboplatin AUC 7. This 1.3% absolute difference had a confidence interval (CI) ranging
7 from -0.7% to 3.5%, meaning that the primary endpoint (exclusion of a 3% difference) was
8 not met (17). Carboplatin AUC 7 was, in other words, **not** non-inferior to RT.

9 The “non-inferiority” issue has already been doubted and criticized by others (7,23). With
10 longer follow-up, the difference in RFR is widening in favor of the RT arm: -1% at 2 years,
11 +1.1% at 3 years (CI: -1 to 3.2%) and + 1.34% at 5 years (CI: -0.7 to 3.5%). The evolution of
12 the hazard ratios (HR) and absolute differences in relapse-free rate, as provided by the data of
13 Oliver et al. (17,22) is shown in figure 1. If one expects 40 relapses per 1000 patients after RT
14 (4%, as reported in reference (22)), the absolute number after AUC 7 could be higher than 70
15 per 1000 (CI + 3.5%) which is an increase of 75%. This difference was confirmed in a
16 retrospective analysis where 1.8% of the irradiated patients relapsed (median follow-up: 9.7
17 years) compared to 8.1% after one cycle of carboplatin (median follow-up: 3.4 years) (24).
18 This high relapse rate was confirmed in other analyses (11,25) where up to 10% of patients
19 relapsed after one cycle of carboplatin with mostly retroperitoneal relapses (11).

20 21 Adjuvant para-aortic radiotherapy nowadays

22
23 Regarding the very low relapse rates after radiotherapy, any attempt to improve the
24 therapeutic ratio should focus on minimizing the adverse effects of RT, including efforts to
25 reduce the risk of SMN (26). Since and even before the Oliver paper (17), several papers
26 concerning improvements in target volume definition, dose prescription and radiation
27 technology have been published (27–30). This raises the question whether RT as used in the
28 paper by Oliver can still be considered contemporary and whether it is scientifically correct to
29 extrapolate the papers’ conclusions, especially those on the development of SMN, into the era
30 of contemporary RT. Others have confirmed the higher incidence of SMN after radiotherapy
31 without providing any detail on radiation dose, radiation volume and technology used while
32 their analysis covered a time span of 25 years and dose schedules, volumes and technologies
33 were generalized under the term “radiotherapy” (31).

1 In general terms, however, it has been demonstrated that the occurrence of SMN after RT is
2 related to irradiated volume, dose and technology.

3 Already in 1999, the randomized TE10 trial demonstrated that PA radiotherapy resulted in the
4 same excellent relapse-free survival rates compared to a DL field, the latter including the
5 ipsilateral pelvic nodes (28). Pelvic recurrence in the PA group was only 1.6% while acute
6 toxicity was lower and sperm count higher in the first 18 months after treatment. The TE10
7 trial concluded that PA radiotherapy should be the standard of care. DL radiotherapy should
8 only be considered in case of un- or maldescended testes or cases of orchiopexy (27). This
9 conclusion confirmed the results two former trials published in 1996 and 1998 (32-33).

10 Treatment field reduction is known to have a major impact on the development of SMN. De
11 Felice et al. reported the risk of SMN to be 6% after a median follow-up of 15 years with only
12 2% of patients dying from this SMN (34). Interestingly, all SMN occurred in patients who
13 received a DL field, while no SMN occurred in the patient group treated with a PA strip. This
14 was also shown by a phantom study (35), where a PA strip RT reduced the induction of SMN
15 by 48 to 63% compared to DL field RT.

16 Considering the up to 60% decreased risk of developing SMN with PA radiotherapy instead
17 of DL field radiotherapy, a subgroup analysis of the patients treated with PA strip alone in the
18 TE19 trial should be performed. Considering table 1 in the 2011 paper (22), the risk of non-
19 GCT SMN was 0.9% in the carboplatin group compared to 1.1% in the RT group (PA and DL
20 combined, no separate information). It seems very unlikely that this difference is of any
21 clinical relevance even when the results on SMN are combined. If an update of MRC TE19 is
22 performed and presented in the future, which we strongly encourage, the distinction between
23 PA and DL RT is necessary.

24
25 The TE18 trial showed the non-inferiority of 20 Gy when compared to 30 Gy (27). It is
26 common knowledge that acute and late toxicity are directly related to radiation dose (36). The
27 same goes for development of SMN. In the MRC TE19 trial, on which the decision to remove
28 radiotherapy from the EAU guidelines was based, the minority of patients received >20 Gy
29 and >50% received 30 Gy. The modeling study mentioned above predicted a 45% reduction
30 in the SMN rate using 20 Gy instead of 30 Gy. It is therefore problematic to extrapolate the
31 data from the TE19 trial to current guidelines without a sub analysis of the patients who
32 received 20 Gy (36% of the cases) versus 30 Gy (54%). For doses above 2 Gy, there is a clear
33 relationship between the risk of SMN with increasing dose (37). Real-life data suggest an
34 increasing risk of SMN with higher doses, and this feature is present to doses even up to 45

1 Gy. This, at least, challenges the dogma that most SMN occur in low or intermediate dose
2 regions (38, 39).

3
4 Indeed, most SMN occur at high-dose regions, meaning that the organ equivalent dose plays a
5 role in the development of SMN. In the MRC TE19 trial, conventional radiation techniques
6 were used, hereby exposing large parts of normal tissue to high doses. With intensity-
7 modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) more normal tissue can
8 be spared from receiving a unnecessary high dose, as has been demonstrated in numerous
9 tumor types (40-42). It is therefore very unlikely that the risk of SMN will be as high with
10 IMRT or VMAT when compared to conventional radiotherapy, in addition to the significant
11 decrease in acute and late toxicity (38).

12
13 This is even more relevant in older patients who have a smaller risk of SMN. Testicular
14 seminoma incidence peaks between 35 to 39 years of age (43). However, 15% occurs after 45,
15 10% after 50 years.

16
17 Even further on the technological evolution line is the advent of proton therapy, which offers
18 the unique combination of adequate target volume coverage and superior sparing of normal
19 tissues due to the characteristics of the Bragg peak (29). In case of stage I seminoma and PA
20 radiotherapy, this means a significantly lower dose to the stomach, small and large intestines,
21 kidneys, spleen, pancreas, bladder and parts of the liver (44, 45).

22 In a direct comparison, Simone et al. demonstrated that the use of proton therapy resulted in
23 superior dose conformity and significant sparing of normal tissues, with highest impact for
24 stomach, bowel, pancreas and liver. They calculated a significant and up to 5-fold drop in
25 development of SMN with proton therapy. For each 50 patients treated with protons instead
26 of photons, 1 SMN would be avoided in a life span of 40 years (44). Additionally, acute
27 toxicity is expected to be significantly reduced with the use of protons (42).

28 29 **Conclusion**

30
31 Adjuvant RT has disappeared from the EAU guidelines in the treatment of seminoma stage I.
32 It is even counter-advised with a grade A recommendation. This decision was based on the
33 results from the MRC TE 19 trial, which claimed carboplatin AUC 7 to be non-inferior to
34 radiotherapy and suggested that RT induced more SMN.

1 The non-inferiority of carboplatin AUC 7 concerning recurrence-free survival is at least
2 debatable as the gap is widening in favor of RT with longer follow-up. The RT technology,
3 dose and treatment field as used in the MRC TE 19 trial are no longer relevant in the era of
4 IMRT, VMAT and upcoming proton therapy. Further updates of the MRC TE 19 trial are
5 urgently needed, with separate analyses of the different RT doses and irradiated volumes
6 used.

7 Ideally the answers come from a prospective, randomized trial, comparing the two treatment
8 arms and using modern RT techniques (with inclusion of proton therapy), with a long follow-
9 up for late side effects and impact on induction of secondary malignancies.

11 Meanwhile, we agree that active surveillance remains the standard of care in most stage I
12 seminoma patients. However, when offering a high-risk patient adjuvant treatment, modern
13 RT is still considered a standard treatment in our centers and is proposed to each patient,
14 along with the use of carboplatin AUC 7.

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FIGURE 1

Fig. 1 Absolute differences in relapse-free rates (RFR) (right) and the corresponding hazard ratios (HR) (left), shown as their evolution over time, with a confidence interval (CI) of 90% (data from the MRC TE19 non-inferiority trial, from Oliver et al.) The CI of the RFR exceeds the 3% after 3 years, therefore the primary endpoint is not met. The HR is greater than 1.0, suggests a trend in favor of radiotherapy.

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