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Journal of Cancer Prevention & Current Research

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Radiotherapy in Seminoma Stage I: the reports of its death are greatly exaggerated

Volume 14 Issue 2 - 2023

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Received: March 08, 2023 | **Published:** March 13, 2023

Introduction

This paper explores the use of radiation therapy in the current landscape of active monitoring (Active Surveillance, AS) and adjuvant platinum chemotherapy for clinical stage I seminoma. Germ Cell Tumors (GCTs) account for 95% of malignant testicular tumors and are classified into seminomas and non-seminomatous tumors. Seminomas are the most commonly occurring type of GCTs, typically developing in the fourth decade of life and representing about 60% of cases. Most patients are diagnosed with stage I disease (75%), while 15% have stage II and 5-10% have stage III disease.

Methods

The recent international literature on the modern management of stage I seminoma was reviewed. The electronic databases Medline, Scopus, and Google Scholar were searched using the terms "seminoma", "active surveillance", "chemotherapy", "radiotherapy", "contemporary management", "secondary cancers", and "secondary malignancies". Also, the National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO), and European Association of Urology (EAU) guidelines for the treatment of testicular cancer were reviewed.

Results

The extent of testicular cancer is determined by the Union for International Cancer Control (UICC) and the International Germ Cell Cancer Collaborative Group (IGCCCG) using staging and risk group categorization. This involves clinical and radiological tests, as well as post-orchiectomy serum tumor marker results such as LDH.[1] Stage I seminoma is defined as a localized cancer that has not spread beyond the testicle to lymph nodes or to distant sites.

For stage I seminoma, orchiectomy with inguinal access is the preferred treatment option. In the past, postoperative choices included radiotherapy, chemotherapy, and active surveillance. However, AS has become the standard approach for patients with stage I seminoma, as orchiectomy alone cures approximately 85% of cases. Adjuvant therapies can lead to unnecessary treatment and expose patients with a high likelihood of survival to severe side effects.[2] Most relapses occur in the first three years under AS protocols, while up to 32% of patients with adverse prognostic factors may relapse after ten years.

While salvage treatments have proven effective, they are also associated with a greater risk of toxicity due to their aggressive nature compared to adjuvant therapies. Risk stratification involves evaluating tumor size (with a 4 cm cut-off) and rete testis infiltration.[3-5] Consequently, it is important to consider adjuvant treatments such as radiotherapy or chemotherapy for patients with a high risk of recurrence. The current debate is whether these two modalities are equivalent in efficacy and which one has less long-term toxicity.

The guidelines from various organizations provide different perspectives on the use of radiation therapy as an adjuvant therapy for stage I seminoma. The National Comprehensive Cancer Network guidelines view radiation therapy as an equal option to active surveillance and chemotherapy.[6] In contrast, the European Society for Medical Oncology guidelines considers it an option only in exceptional cases, such as when carboplatin cannot be administered due to bone marrow failure or severe cardiovascular comorbidity.[1,7] The European Association of Urology guidelines recommends carboplatin only as an appropriate adjuvant therapy, citing the increased risk of secondary cancers associated with radiation therapy.[8] Adjuvant radiotherapy should be used selectively, reserved only for patients unsuitable for surveillance and for whom chemotherapy is contraindicated.

The recommendations are primarily based on the MRC TE 19 study by Oliver et al., which compared carboplatin AUC7 with radiation therapy in patients with stage I seminoma.[9] At the 2-year follow-up, the relapse-free rate (RFR) difference between radiotherapy and chemotherapy was -1% (90% CI, -2.5 to 0.5), concluding that adjuvant carboplatin was non-inferior to radiotherapy with a pre-specified non-inferiority threshold of 3%. However, the 5-year results of the same study published in 2011 showed that RFR rates were −1.3% (90% CI, −3.5 to 0.7), demonstrating non-inferiority only when the threshold was adjusted to 5%. Moreover, most recurrences in patients who received chemotherapy were in the retroperitoneum, emphasizing the importance of imaging this space during follow-up for high-risk chemotherapy patients. As a result, radiation therapy as an adjuvant treatment for stage I seminoma has declined in recent years.[10-12]

According to research by Powles and colleagues, there was a non-significant increase in mortality over a period of nine years following the administration of carboplatin in the context of ischemic heart disease and cerebrovascular events.[13] Additionally, they could not confirm the lower incidence of secondary cancers, which is often considered a benefit of chemotherapy compared to radiation therapy. In a large multicenter patient series that included 6042 patients with testicular cancer treated between 1976 and 2006, Groot et al. studied the risk of mortality from malignant disease relative to the general population.[14] Patients with seminoma had 2.5 - 4.6 times increased mortality from stomach, pancreas, bladder, and leukemia neoplasms. Radiation therapy and chemotherapy were associated with a 2.1x

(95% CI, 1.8-2.5) and 2.5x (95% CI, 2.0-3.1) higher risk of mortality from a second malignancy, respectively, compared to the general population. In multivariate analysis, patients treated with platinum had a 2.5-fold increased hazard ratio (HR; 95% CI, 1.8-3.5) compared to those who did not receive platinum. This risk increased by 0.29 (95% CI, 0.19-0.39) for every 100 mg/m^2 of platinum administered ($p < 0.001$). Moreover, there was a 2.1-fold increase (95% CI, 1.5-4.2) in mortality from ischemic disease after platinum administration compared to patients not exposed to platinum. As a result, platinum chemotherapy was found to carry a dose-dependent risk of mortality from secondary cancer, although a causal link is yet to be established. In a retrospective study of 451 patients with stage I seminoma, of whom 243 received adjuvant therapy, Guido Ruf et al. found that carboplatin carried a 2.4-fold increased risk of secondary cancer compared to 2.7 for radiotherapy.[15] Although the analysis has some weaknesses, and the patients were treated between 1994 and 2014, it raises critical questions.

In treating testicular seminoma, radiotherapy has traditionally involved irradiating both para-aortal (PA) and ipsilateral pelvic lymph nodes, the so-called dog-leg field. However, a clinical trial was conducted to compare pelvic and PA to PA-only irradiation in 478 patients with clinical stage I seminoma, and it was found that PA-only irradiation resulted in low relapse rates and reduced side effects, making it the recommended standard treatment.[16] Reducing the irradiation area has been shown to significantly impact the development of secondary malignancies.[17] In the same spirit of treatment de-escalation, the TE18 trial aimed to determine if reducing radiation therapy doses in patients with stage I seminoma was possible without compromising efficacy. During the study, patients underwent random assignment to receive either 20 Gy/10 fractions over two weeks or 30 Gy/15 fractions over three weeks following orchiectomy. After a follow-up period of 61 months, there was no significant difference in relapse rates between the two groups. Like treatment field size, radiation dose determines acute and late toxicity. These two facts, i.e., limited treatment fields and dose de-escalation, will likely reduce the risk for secondary cancers when radiation is used.

Patient education is a critical tool in the early detection and management of testicular cancer, since there is no widely accepted screening test for the disease. Educating patients on the signs and symptoms of testicular cancer, such as a lump or swelling in the testicle, pain or discomfort in the scrotum, or heaviness in the lower abdomen, might encourage them to seek medical care early on. Also, providing information on testicular self-exams will likely help diagnose cancer when is localized and cure is much more likely with less intensive treatments.

New biomarkers hold the potential to become valuable tools in individualizing treatment for seminoma patients. By providing a more accurate assessment of the patient's disease status and anticipated response to some treatment, be it radiotherapy or chemotherapy, biomarkers may aid clinicians to tailor treatments to the individual patient's needs, sparing unnecessary toxicity. Examples of such biomarkers include circulating miRNAs[18] or cell-free DNA.[19]

Conclusion

The non-inferiority of single-dose carboplatin AUC7 versus radiotherapy is debatable, as the difference between the two treatments widens as the follow-up interval increases. Also, radiation therapy technology has improved significantly, and the irradiated volumes have decreased, thus decreasing the estimated probability of secondary cancers. The optimal approach for stage I seminomas remains active surveillance. However, for patients with unfavorable factors and a high risk of recurrence, there is a need for a modern prospective randomized study comparing state-of-the-art radiotherapy vs. chemotherapy.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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Citation: Kamperis E, Kodona C, Papalexandrou A, et al. Radiotherapy in Seminoma Stage I: the reports of its death are greatly exaggerated. *J Cancer Prev Curr Res*. 2023;14(2):35–37. DOI: 10.15406/jcpcr.2023.14.00515

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