Radiotherapy in testicular germ cell tumours – a literature review

Joanna Jonska-Gmyrek, Piotr Peczkowski, Wojciech Michalski, Grazyna Poniatowska, Agnieszka Zolciak-Siwinska, Beata Kotowicz, Pawel Wiechno, Magdalena Golawska, Maria Kowalska, Tomasz Demkow

Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland

Testicular germ cell tumours (GCT) represent about 1–2% of malignant in men. The essential therapeutic option for early-stage GCT is radical orchiectomy (RO), except in situations that require immediate chemotherapy in patients with a massive dissemination and unequivocally elevated levels of tumour markers.

Postoperative radiotherapy (PORT) in patients with testicular seminoma in Clinical Stage I (CS I) is one of the treatment options next to active surveillance (AS) and chemotherapy (CHTH). Regardless of the procedure, five-year survival in this group of patients ranges between 97% and 100%. In the article, we present the literature review pertinent to therapeutic options, with a focus on radiotherapy. We have searched MEDLINE (PubMed) for all studies on patients with GCT treated with radiation therapy during the last 20 years, and the current therapeutic recommendations. We used the following keywords: germ cell tumours, testis, seminoma, non-seminoma, radiotherapy, outcome.

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Introduction

Germ-cell testicular tumours (GCT) represent about 1–2% of all male malignancies, 60% of which are seminomas. Among this group, about 80% of patients present stage I of the disease, and about 15% have stage II [1, 2]. Radical orchiectomy (RO), followed by staging studies such as abdominal-pelvic-thoracic computed tomography (CT), is an essential diagnostic and therapeutic option for GCT, except in situations that require immediate chemotherapy (CHTH) in patients with massive dissemination and unequivocally elevated levels of tumour markers [3].

Regardless of the procedure, the five-year survival in this group of patients ranges between 97% and 100%, as demonstrated in numerous publications [2–9].

During the median 15-year follow-up of 85 patients, 20-year overall survival (OS) and disease-free survival (DFS) rates were 92% and 96.3%, respectively [10].

Postoperative radiotherapy (PORT) has long been considered the standard treatment in early testicular seminoma; however, recently alternative strategies such as active surveillance (AS) and CHTH are being considered [7, 11–13]. Postoperative CHTH using carboplatin is a treatment as effective as PORT [13], but seminoma has a tendency for loco-regional recurrence.

In the T19 trial, 1477 patients with testicular seminoma CS I were randomly assigned to a single dose of carboplatin at a dose seven times the area under the curve. During the median follow-up of 6.4–12 years, the authors identified non-inferiority of carboplatin and irradiation [14].

In the study presented by Cohn-Cedermark *et al*., 14.3% of recurrences were reported in the group with AS, while in the group after PORT this figure was only 0.8%, and the five-year OS of patients with seminoma in CS I amounted to 99% [15].

From 12,075 patients taking part in 13 trials, reported by Petrelli *et al*., PORT or CHTH reduced relapse rates to 3.9%, while in the AS arm 14.8% of relapses were confirmed. Adjuvant treatment significantly improved five-year DFS ($p < 0.00001$), but not OS ($p = 0.94$) [16].

The analysis of the 33,094 patients with seminoma in CS I demonstrated a slight OS advantage in patients who had undergone PORT when compared with AS group, with 93.5% vs. 95% (HR 0.58, $p < 0.0005$) rates, respectively [17].

In the group of 282 patients with seminoma in CS I, treated between 1997 and 2013, reported by Bilici *et al*., 130 (46.1%) patients received PORT. During the five-year follow-up, the OS of the AS group was lower when compared with adjuvant treatment patients, but statistical difference was not demonstrated [18].

Researchers who prefer AS as an option in testicular seminoma CS I, indicate only a slight difference in the OS of patients undergoing adjuvant therapy, while stressing the possibility of obtaining a high percentage of curability

after the application of salvage radiotherapy or CHTH in the case of recurrence. The risk of relapse after PORT is estimated to be only about 3–5%, compared to the relatively high rate of relapse of 15–20% in AS patients during the follow-up period [19].

In the analyzed group of 2437 patients with seminoma in CS II, the application of PORT was as follows: CS IIA – 78.1% of patients, CS IIB – 54.4%, and CS IIC – 4.2%. During the 65-month follow-up of patients with CS II A and II B, PORT demonstrated a statistically significant superiority when compared to the CHTH in CS II A. The 5-year OS was as follow: IIA – 99% vs. 93% (p = 0.027), IIB – 95.2% vs. 92.4% [20].

Taking into account the survival rates of patients with early testicular seminoma, we should consider the risk of late sequelae after radiotherapy. Recent radiotherapy developments, such as intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), and proton therapy (PT), seem to be promising methods. They may be applied to reduce acute and side effects (IMRT, VMAT) [6, 21] and minimise the risk of secondary malignancies in younger patients (scanning proton therapy) [23].

According to the literature, the main problem arising from the use of IMRT is an increased risk of secondary malignancies [24–29], and from proton therapy, limited availability of this therapeutic method. So far, we use the above methods in particular clinical situations in patients with GCT.

Rules of radiotherapy in GCT

Treatment volume

The irradiation area in testicular seminoma CS I had been reduced from the traditional dog-leg, consisting of para-aortal (PA) and ipsilateral pelvic lymph nodes to the PA area [18, 30, 31].

Taking into the consideration the relatively low risk of positive pelvic lymph nodes in stage I, a clinical trial comparing pelvic and PA to PA only irradiation was conducted. The treatment group consisted of 478 patients with CS I seminoma. As a result, 3.4% of relapses were confirmed in the group with extended field irradiation, and in 4% of patients irradiated to PA volume only. Pelvic recurrences were confirmed in 1.6% of patients irradiated to PA volume, while none among those treated to an extended field recurred. Considering the low relapse rate with either treatment and reduced gonadal, haematological, gastrointestinal toxicity, as a standard treatment in these patients, PA irradiation is recommended [32]. The inferior border of irradiated volume at mid-pelvis helps to prevent the nodal recurrences and to avoid treating the prostate and bladder. Testicular tumours located at the left side tend to relapse around the insertion of the left testicular vein into the left renal vein, so the left para-aortic region has to be included in the irradiated volume [2].

Treatment dose

In the 1980s and 1990s, the PA lymph nodes and ipsilateral pelvic nodes in CS I were irradiated up to a dose of 35 Gy. In CS II, mediastinal lymph nodes up to 30 Gy and the left supraclavicular area up to 40 Gy was irradiated [30, 33].

Since then, the therapeutic dose decreased to 20–25 Gy in CS I and to 30–36 Gy in CS II [34].

The percentage of PORT using a low dose increased from 1.5% in 1999 to 34% in 2012 [17].

To compare the outcome of dose 20 Gy in 10 fractions to 30 Gy in 15 fractions, randomised trials (Medical Research Council): TE10, covering 478 patients and TE18, covering 1094 patients, were conducted. In the TE10 trial, patients were randomised to PA or PA and ipsilateral iliac fields and irradiated up to the dose of 30 Gy. In the TE18 trial patients received PA radiotherapy up to 20 or 30 Gy. Five-year relapse rates were as follow: 3% and 3.6%, in the 30 Gy and 20 Gy arms, respectively. Five-year relapse-free rates were as follow: 95.1% for 30 Gy and 96.8% for 20 Gy. During the seven-year follow-up, non-inferiority of 20 Gy to 30 Gy was demonstrated [14, 17].

The recommended adjuvant RT dose in CS I testicular seminoma is 20 Gy in 2 Gy fractions [2].

A meta-analysis presented by Giannatempo *et al*., including 900 patients with testicular seminoma CS IIA and CSIIB, treated with PORT (607) and CHTH (283), demonstrated relapse rate similar in both arms in CS IIA, but in CS IIB, CHTH was more favourable [35].

Radiotherapy in CS II can be performed if the nodule diameter does not exceed 3 cm [2].

Recurrent disease

In the case of irradiation performed at relapse, a minimum of 30 Gy delivered to small masses to PA and pelvic area and up to 36 Gy to gross disease is recommended. The dose over 36 Gy does not improve the therapeutic index [2].

Radiotherapy planning

Postoperative radiotherapy (PORT)

Radiotherapy should be commenced after the orchiectomy wound has healed. Protecting the healthy testicle is recommended for all patients. Irradiation is carried out five times a week with antiemetics administered two hours before radiotherapy. During the therapeutic decision, we must be aware of contraindications for radiotherapy, such as horseshoe or pelvic kidney, inflammatory bowel disease, or previous radiotherapy of the abdomen/pelvis.

Planning radiotherapy is based on a CT scan without contrast. During the planning process, the anatomical structures may be used.

CS I

Upper and lower limits can be based on anatomical structures. The upper border on TH11, lower edge on the bottom of L5. The total dose is 20 Gy in 10 fractions. In the case of pelvic surgery due to, for example, an undescended testicle or inguinal hernia, the iliac lymph nodes, and inguinal and postoperative scar on the side of the testicular tumour should be included in the area of the treatment.

Table 1. Testicular seminoma, treatment options, radiotherapy principles [3, 14]

	Stage I	Stage II	Stage III
I line treatment	Low risk: Preferred option: AS Alternatively: Carboplatin (AUC 7) 1× RT (para-aortal region) 20 Gy/10 Fr High risk: Preferred: AS Carboplatin (AUC 7) 1× Alternatively: RT 20 Gy/10 Fr	II A BEP × 3 lub EP × 4 RT (Para-aortal and ipsilateral pelvic lymph nodes) 20 Gy/10 Fr + boost 10 Gy/5 Fr IIB/IIC BEP x3 Contraindications to CHTH: RT (Para-aortal and ipsilateral pelvic lymph nodes) 20 Gy/10 Fr + boost 16 Gy/8 Fr)	BEP × 3-4 (VIP × 3-4)
Residual disease	NA	Observation In the case of tumours > 3 cm: PET +/– biopsy or resection	Observation In the case of tumours > 3 cm: PET + biopsy or resection
Recurrent disease	After carboplatin or Observation: RT BEP × 3–4 After RT: BEP × 3(EP × 4)	Salvage CHTH In a local relapse: RT In case of single resectable tumour: * Surgery	

AS – active surveillance; Fr – fraction; Gy – Gray; RT – radiotherapy; BEP – bleomycin, etoposid, cisplatin; EP – etoposid, cisplatin; VIP – vepesid, iphosphamide, paclitaxel; PET – positron emission tomography, 1× – one course; NA – non applicable

CS II

When irradiating pelvic lymph nodes (modified dog leg), the upper border is the same as in CS I; the lower is the bottom of the upper edge of the acetabulum on the side of the removed testicle. The initial dose is 20 Gy in 10 fractions, with an increase of the dose to 30 Gy at the involved lymph nodes in CS IIA, and to 36 Gy in CS IIB [2].

The area of irradiation includes: CTV (Clinical Target Volume): aorta, vena cava + 1.2–1.9 cm of therapeutic margin. PTV (Planning Target Volume): covers CTV + 0.5 cm.

During the planning process, the dose-volume histogram must be respected, taking into the consideration the organs at risk (OAR), such as stomach, colon, kidneys, pancreas, and liver [24]. No more than 50% of each kidney may receive 8 Gy. In the presence of one kidney, no more than 15% of an organ may receive 20 Gy.

The risk of early radiation-induced complications has been reduced due to technical radiotherapy development, such as IMRT and VMAT, and the recent availability of spot scanning proton therapy. The risk of secondary cancers connected with 3D technology is lower when compared to the IMRT [3].

In all cases, because of the dose delivered to OAR, the recommended technique is based on three-dimensional conformal radiotherapy (3D-CRT) planning.

Palliative radiotherapy

Palliative radiotherapy (PR) is indicated in the following cases: non-seminomatous tumours – symptomatic treatment. In metastatic disease, irradiation to the area of metastasis, such as bone, spinal cord, central nervous system.

Table 2. Testicular non-seminoma, radiotherapy principles, therapeutic options [3, 14]

CS I, II, III, IV/ Disqualification from CHTH/surgery	Indication/dose
Palliative treatment	Spinal cord compression: RT 20 Gy in 5 fractions shielded by steroids Brain metastases: radiation to the brain volume: 45 Gy in 25 fractions or 20 Gy in 5 fractions Pineal germ cell tumour: radiation throughout the axis is necessary if it is allowed by the general condition of the patient Painful bone metastases: 8 Gy in one fraction or 20 Gy in 5 fractions, depending on the life expectancy

CS – clinical stage; RT – radiotherapy; CHTH – chemotherapy; Gy – Gray

The dose depends on the general location and size of infiltration. Irradiation to the total dose of 20 Gy in five fractions or radical dosage, 45 Gy in 25 fractions, is performed.

General guidelines for the treatment of testicular germ cell tumours are presented in Table 1 and 2.

Treatment-related sequelae

In the study presented by Cerkaska-Gluszak *et al*., haematological complications, such as anaemia and leukopaenia, according to dose fractionation, caused the treatment discontinuation in 23.4% of patients. Digestive tract sequelae, like nausea, vomiting, and diarrhoea, according

to the size of the irradiated volume and the fractionation dose, occurred in 28% of patients and caused the treatment discontinuation in 16.8% of patients. Another malignancy, influenced by the time after irradiation and the irradiated volume was doubled after ten years [23].

The authors observed one death resulting from exceeding the dose in the group treated at our centre, but apart from that, no nausea, vomiting, or haematological complications requiring the discontinuation of treatment were reported [33].

In the therapy of testicular GCT, observation plays an important role, aiming at detection of relapse as well as late sequelae, including secondary malignancies. When considering PORT as a method of adjuvant therapy, the risk of both acute (early) and chronic (late) radiation complications is an important issue [27, 29].

Long-term observations suggest an increased risk of secondary tumours located in the gastrointestinal tract, bone marrow, the bladder, and the other testicle [5, 6, 33, 36]. The likelihood of leukaemia also increases because of irradiation of the pelvic bones and the fractionation dose [32, 37].

The study including 29,356 white testicular cancer patients and 621 cases of second malignancies, reported by Schairer *et al*., led to the conclusion that the mortality from second cancers following irradiation concerned only a group of patients treated in the seventies, when chest radiotherapy was an option [26].

In the study presented by Mazonakis *et al*. the risk of second malignancy in a typical 39-year-old individual treated with PORT was estimated at the age of 70 years for stomach, colon, liver, pancreas, and kidney, as 4.2, 11.39, 0.91, 3.04, and 0.14, respectively, per 10,000 people [24].

Over the past 20 years, the risk of radiation-induced reactions connected with a reduction of the irradiated area and the total dose had been significantly reduced. Determining complications of treatment is an essential part of the therapeutic process and follow-up of patients with GCT. Because of limiting the irradiation field, the currently observed radiation reactions are minor and usually do not require discontinuation of radiotherapy [5].

To reduce the acute and side effects, novel techniques, such as IMRT and spot scanning proton therapy, may play a role in particular clinical situations, such as one kidney, and other, needing tissue sparing. These methods, however, have limitations in the use of patients with testicular GCT, due to long life expectancy, the risk of second malignancies connected with IMRT, and low availability of proton scanning therapy.

Technical radiotherapy developments

Intensity-modulated radiation therapy (IMRT), spot scanning proton therapy (PT), and volumetric modulated arc therapy (VMAT) represent the advanced treatment methods, which are based on X-rays and heavy ion.

Intensity-modulated radiotherapy

Intensity-modulated radiation therapy is an external beam technique of irradiation, commonly used to treat a range of cancers. Using IMRT, we can achieve a high dose to the treated area with highly conformal radiation delivered from the specified number of beam angles.

Intensity-modulated radiation therapy, sparing healthy tissues, allows a particular dose to concentrate in the tumour volume. However, it has the potential to increase the number of radiation-induced second malignancies. This happens because of more monitor units and larger dose to the total body, due to leakage radiation and because of more fields in IMRT. A greater volume of healthy tissue is irradiated with lower radiation doses. In long-term survivors, IMRT may double the radiation-related second cancer. This option may be favourable for older patients for improvement of local control and to reduce the early toxicity in a patient with one kidney or too large volume of liver contained in the irradiated area, after balancing the risk. Due to the above properties, IMRT is not acceptable for children [21, 27].

Volumetric Modulated Arc Therapy

Volumetric modulated arc therapy radiotherapy is a variant of IMRT, in which radiation is delivered in a continuous manner as the treatment gantry rotates around the patient, instead of delivering radiation from several beam angles. A disadvantage of this variation is a greater spread of low-dose radiation in healthy tissues.

According to the authors' knowledge, we have no literature data about the VMAT implementation in testicular seminoma treatment.

In the study performed by Martin *et al*., among 12 cases of prostate cancer, the mean dose delivered with VMAT was higher than the dose delivered with IMRT. The difference was 4.3 Gy (p = 0.019) and was statistically significant [38].

Spot scanning proton therapy

Proton therapy (PT) may offer a substantial clinical advantage over photon therapy because of the unique depth dose characteristics of protons. The result is the significant reduction of doses to adjacent critical structures proximal and distal to the target volume. This may allow escalation of doses delivered to the tumour and normal tissue sparing, leading to better local control and survival, and reducing at the same time toxicity and improving quality of life. This is possible only if the proton machine employs the pencil scanning beam, which avoids the production of neutrons and reduces the dose delivered to the total body. The patient gets a benefit of protons if the scanning beam with doses ten times lower than IMRT is used [27, 28]. Due to its properties, proton therapy is recommended for paediatric cancers, ocular melanoma, chondrosarcomas, and chordomas [39].

In the study by Hoppe *et al*., proton therapy reduced the mean dose to ipsilateral kidney, pancreas, stomach, bowel space, colon, and small intestine when compared with 3D radiotherapy and IMRT [22].

In the study presented by Chung *et al*., reporting the outcome of 558 proton therapy patients and 558 photon therapy patients, second cancers occurred in 29 patients treated with protons and in 42 patients treated with pho-

tons. After adjusting the factors such as sex, primary site, age at treatment, and year of diagnosis, proton therapy was not connected with an increased risk of secondary malignancies [28].

Summary

Testicular seminoma has a favourable prognosis regardless of the treatment after orchiectomy. In testicular seminoma CS IA and IB, AS is now recommended, next to carboplatin CHTH or PORT, depending on the clinical situation and the patient's preferences.

Indications for adjuvant RT in CS I may be debatable. The European Association of Urology (EAU), in contrast to the NCCN, does not recommend radiotherapy especially in men < 40 years of age [11, 30]. Follow-up compliance based, among others, on the study of tumour markers and modern diagnostic imaging plays a role in the selection of treatment.

Radiotherapy is preferred in testicular seminoma CS II A, whereas in CS II B chemotherapy is the treatment of choice.

Modern radiotherapy based on 3D planning systems allows a precise definition of the irradiation fields, which spares critical tissues and organs. Reducing the dose and area treated has led to improved tolerability and reduction of late complications, but there is still an increased risk of secondary malignancies, which is essential for long-term survivors. The recent development of proton therapy seems to be a good option for a proper dose delivered to the tumour with optimal tissue sparing and no increased risk of second malignancies, but greater availability and results of randomised studies evaluating this approach are needed.

The authors declare no conflict of interest.

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Address for correspondence

Joanna Jonska-Gmyrek
Maria Skłodowska Curie Memorial Cancer Centre
and Institute of Oncology
Roentgena 5
02-781 Warsaw, Poland
e-mail: jonska@wp.pl

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