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Review

Radiotherapy for Stage IIA seminoma: The Northern Israel Oncology Center Experience, 1971–2010

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ABSTRACT

Aim: To evaluate treatment details, outcome, relapse rate and side-effects in Stage IIA seminoma irradiated and followed for a period of 39 years.

Background: Seminoma is a very radiosensitive disease and radiation therapy alone is able to achieve long-term disease-free survival, even in advanced Stage disease. Due to the lack of long-term prospective studies, it is of value to follow patients and try to determine the appropriate volume to be irradiated and the dose which can achieve total cure with minimal acute and chronic side-effects.

Patients and methods: A retrospective review of 24 Stage IIA seminoma patients irradiated between 1971 and 2010 was performed. All patients underwent orchiectomy and meticulous clinical, biochemical and radiological staging.

Results: Median age at diagnosis was 36 years and median follow-up was 84 months. A majority of patients received the "hockey-stick" irradiation schedule (para-aortic lymph nodes and hemi-pelvis) to a total dose of 2250–2500 cGy and a boost to radiologically involved nodes of 500–1000 cGy. Treatment was well-tolerated. Twenty-one (88%) patients are alive with no evidence of disease. Two patients died due to unknown causes, while one patient died due to head of the pancreas carcinoma, most probably radiation-induced.

Conclusions: In Stage II seminoma, radiotherapy can provide excellent results with low rates of toxicity. Reduction of total dose and size of fields without affecting the good results should be considered. Due to prolonged survival, awareness of second primary tumor is indicated.

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1. Background

Testicular seminoma accounts for 40% of primary testicular neoplasms, with 70–85% of patients presenting with disease confined to the testis (Stage I), while 15–20% present with infra-diaphragmatic lymphadenopathy (Stage II).[1] Due to the high radiosensitivity of seminoma, radiotherapy has become the mainstay of treatment in limited nodal involvement.[1,2] Cause-specific survival usually exceeds 90% and, in recent years, has been approaching 100%. Relapse rates reported in the literature vary according to stage and treatment modality with 11%, 19%, and 39% in Stage IIA, IIB, and IIC, respectively.[1] Stage IIB (2–5 cm in size lymph nodes) can be treated successfully with platinum-based chemotherapy or high-dose radiotherapy to high-volume fields with chemotherapy held for relapse. In this retrospective study, we review our clinic's experience in radiotherapy treatment, outcome and toxicity in 24 Stage IIA post-orchiectomy seminoma patients over a period of 39 years.

2. Patients and methods

We report the radiotherapy treatment of 24 Stage IIA testicular seminoma patients, treated successfully with radiotherapy. Median age at diagnosis was 36 years (range, 23–58 years) (Table 1

). Preoperative staging consisted of family history, anamnestic details concerning prior diseases or surgical procedures in pelvic or inguinal regions, physical and neurologic examination, testicular ultrasound, blood count, biochemistry profile including measurement of B-human-choriogonadotropin (β-HCG), alpha-feto-protein (AFP) and lactate dehydrogenase (LDH) (Table 2). The majority of patients presented preoperatively with painless testicular swelling or mass for a mean duration of symptoms of three months. Post-orchiectomy staging consisted of whole-body computerized tomography (CT scan) for all patients diagnosed after 1980. In the last 10 years, eight patients have undergone fluoro-deoxyglucose positron emission tomography (PET-CT) as a part of staging. Before 1980, lymphography was used as the main goal of staging. Staging was determined using the American Joint Committee on Cancer (AJCC), 7th edition: Stage IIA with pathologic abdomino-pelvic lymphadenopathy up to 2 cm in size.

Radiotherapy was delivered either with cobalt-60-teletherapy (two patients before 1994) or with 6–18 MV linear accelerator (Linac). Treatment decision parameters and irradiated volume were done according to Wilder et al.[3] Irradiated volume included the para-aortic lymph nodes (upper field: interface T12/T11; lower border: bottom of L5; width: 9–11 cm). The ipsilateral hemipelvis was irradiated ("hockey-stick" method) in 20 (83%) patients, with the lower border downward to the mid-obturator level. Since 1990, the hemipelvis field has been omitted and the lower border set at the cranial rim of the ipsilateral acetabulum (Fig. 1A and B).[4] The whole pelvis ("inverted-Y" method) was irradiated in three patients due to scrotal violation and previous inguinal repair in the presence of an undescended testis.

Table 1 – Anamnestic details, symptoms, diagnostic and therapeutic measures.

Age [years], median, range	36, 23–58
	# of patients
Religion	
Jews	22
Moslem	1
Christian	1
Ethnic origin	
Ashkenazi Jews	23
Sephardic Jews	1
Place of birth	
Israel	17
Europe	3
North Africa	2
North America	2
Referring hospital	
Rambam	10
Jerusalem (Hadassah)	4
Safed	3
Nahariya	3
Haifa (Bnei-Zion)	2
Haemek	2
Etiology	
Cryptorchidismus	2
Torsion	1
Side of tumor	
Left	16
Right	6
Bilateral	2
Symptoms	
Hard, painful testicle	5
Testicular swelling	12
Slow growing, painless mass	7
Duration of symptoms (months)	
Median	77
Range	1–12
Work-up	
Tumor markers[a]	
β-HCG	23
LDH	6
Radiology	
Testicular US	15
CT scan	23
PET-CT	9
Lympho-angiography	7
Abdominal US	2
Mode of surgery	
Inguinal orchiectomy	23[b]
Scrotal orchiectomy	1
Pathology	
Classical seminoma	23
Anaplastic seminoma	1
ITGCN	7[c]
Stage of disease	
IIA	24
Schedule of radiotherapy	
total/daily dose (cGy)/# treatments	
Hockey Stick	
2500/125/20	11
3000/200/15	2
2550/170/15	3
2550/150/17	1
2250/150/15	1
2250/170/13	1
2000/125/16	1

Table 1 (*Continued*)

	# of patients
Inverted Y	
2400/200/17	1
3000/200/15	1
4000/250/16	1
Upper/lower abdomen	
1250/125/10	1[d]
Boost (involved lymph nodes)	
1000/200/5	4
1000/125/8	6
510/170/3	5
600/200/3	2
1400/125/12	1
450/150/3	1
900/150/6	1
500/125/4	2
Boost to scrotum	
2600/200/13	1
Mediastinum/supraclavicular grooves	
3500/250/14	1
3000/200/15	1

[a] Alpha-feto-protein was negative in all patients.
[b] Patient #3 initially underwent biopsy from an inguinal mass which proved to be an undescended testicle and then orchiectomy.
[c] Intratubular germ cell neoplasm.
[d] Retrospectively, it was IIB disease. Besides the upper/lower abdomen, scrotal (3000 cGy/200/15) and para-aortic/pelvic regions were also boosted with 2000 cGy (100 cGy daily fraction). Mediastinum/both supraclavicular grooves received a total dose of 3000 cGy (daily fraction 200 cGy).

Total dose ranged from 2000 to 4000 cGy, with daily fractions of 200–250 cGy.

Since 1980, dosages have been in the range of 2250–2550 cGy, with a total dose median of 2500 cGy (daily fractions of 150–200 cGy). Treatment was followed by a boost to the involved lymph nodes. Patients were boosted to a range of 450–1400 cGy (median, 900 cGy; daily fractions 125–200 cGy). Two patients received prophylactic mediastinal and supraclavicular irradiation ranging from 3000 to 3500 cGy (daily fractions 200–250 cGy). One patient was irradiated to the upper/lower abdomen to a total dose of 1250 cGy with daily fractions of 125 cGy. One patient was boosted to the scrotum (total dose of 2600 cGy; with daily fractions of 200 cGy).

Generally, patients were followed by three-monthly intervals for the first two years with physical examination, serum tumor markers and chest X-rays (CXR), and CT scan of the abdomen/pelvis. Thereafter, follow-up was continued at six-monthly intervals to year 5 and annually beyond this.

Overall survival (OS) was determined from the date of radiotherapy completion to the last available clinical follow-up. The latest date and status were evaluated directly via the Ministry of Internal Affairs (Fig. 2).

3. Results

Between January 1971 and March 2010, 24 Stage IIA seminoma patients were included in this retrospective study. Median time to follow-up was 84 months (range, 42–282 months). Median age was 36 years (range, 23–58 years). The majority (90%) were of Jewish ancestry and Israeli-born (75%). Cryptorchidismus as an etiologic factor was observed in two patients. A left-sided tumor was observed in 16 patients, right-sided in six, and there were two patients with bilateral tumors. All patients presented with swelling or a palpable hard testicular mass and US demonstrated the typical ultrasonographic features of a malignancy. Mean duration of symptoms was in the range of 1–12 months. Seven patients were diagnosed with incidental ITGC in addition to their seminoma, findings which did not influence negatively their prognosis.

All patients completed their scheduled radiotherapy without interruption. Acute side effects were mild and dominated by grade I nausea and temporary weakness. Late toxicity is shown in Table 2. Only one patient (#9) developed a second primary; three years after completion of his scheduled radiation

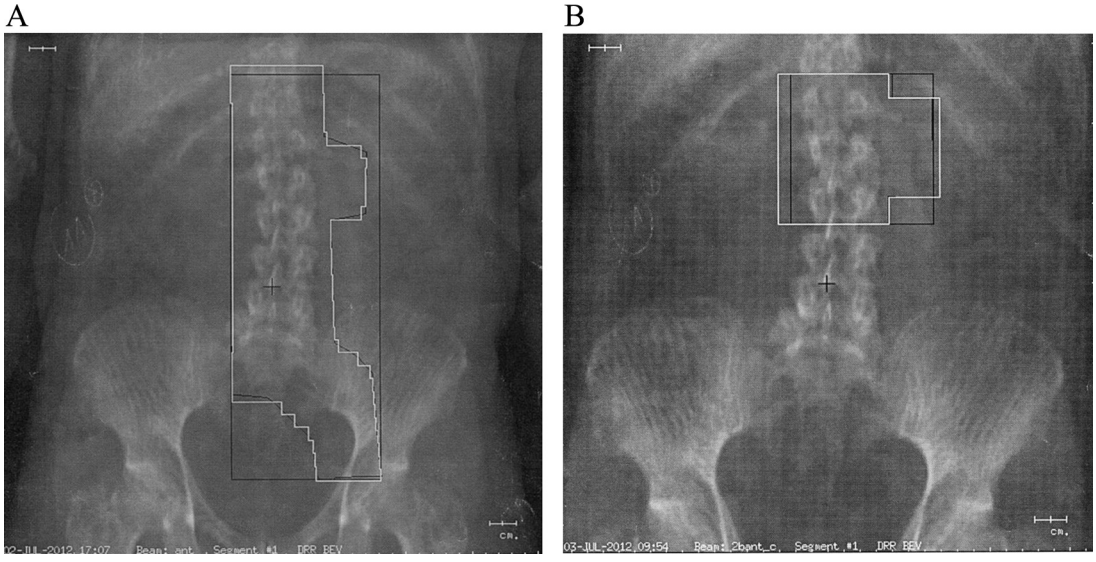

Fig. 1 – Treatment portal used for Stage IIA seminoma: primary para-aortic and ipsilateral, upper iliacal lymph nodes (A) plus boost to radiologically involved lymph nodes (B).

Table 2 – Treatment schedule, side effects and follow-up.

Pt. no.	Radiotherapy schedule		Dose (total/daily fractions/no. of fractions)			
	Facility	Plan		Side effects	Latest date	Status
1.	18 MV	1. Hockey-stick	3000/200/15	2nd primary radiation-induced pancreatic carcinoma	19/05/2002	DOD[a]
	18 MV	2. Boost	600/200/3			
2.	6 MV	1. Hockey-stick	2250/170/13	Peptic ulcer disease	23/03/2010	NED[a]
	6 MV	2. Boost	510/170/3			
3.	6 MV	1. Hockey-stick	2550/170/15	Radiation-induced proctitis (mild form)	13/12/2009	NED[a]
	6 MV	2. Boost	510/170/3			
4.	6 MV	Upper abdomen	1250/125/10	Chronic abdominal pain	18/02/1988	NED[a]
		Lower abdomen	1250/125/10			
		Par-aortic + pelvis	2000/100/10			
	CO^{60}	Scrotum	3000/200/15			
	6 MV	Mediastinum + supraclavicular grooves	3000/200/15			
5.	18 MV	1. Hockey-stick	2500/125/20	Neutropenia, thrombocytopenia (self-limited)	01/12/2012	NED[a]
	18 MV	2. Boost	500/125/4			

[a] DOD = dead of disease (radiation-induced primary); NED = no evidence of disease.

therapy, he developed a Helicobacter positive duodenal ulcer and was treated conservatively. Three years later, the ulcer recurred massively with perforation. The patient underwent emergency laparotomy which revealed massive pancreas head carcinoma, involving the ulcerated part of the duodenum. A Whipple procedure was accomplished successfully but his tumor recurred abdominally some months later, he deteriorated and died. Reviewing the records of the Ministry of Internal Affairs revealed that 21 (88%) patients are alive with no evidence of recurrent disease or second primary. They were followed in other hospitals or by their general practitioners.

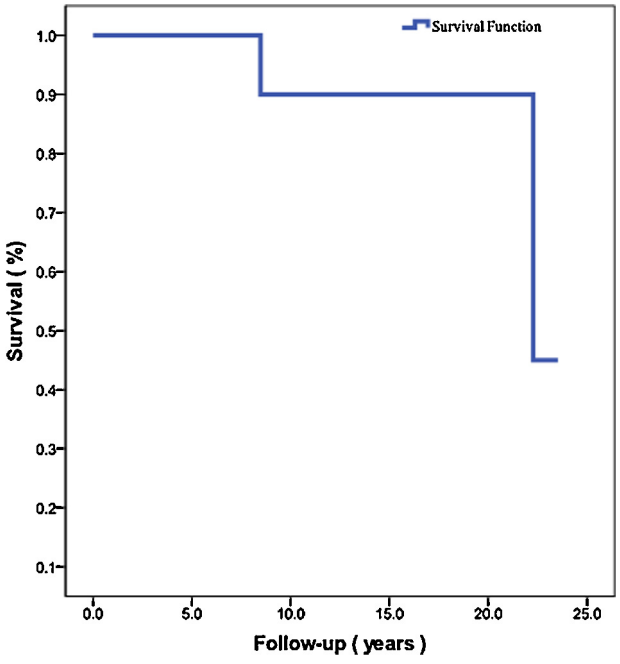

Fig. 2 – Survival curve of 23 Stage IIA seminoma patients.

4. Discussion

Despite the current use of lower radiation doses and smaller field sizes, our retrospective study confirms the excellent outcome of Stage IIA, non-bulky, seminoma that has remained excellent over the long term. However, work-up after orchiectomy demonstrated that about 15–20% have radiologically involved para-aortic lymph nodes and 70% even small bulk disease,[5,6] albeit the number of Stage IIA disease patients has been too small to mount Phase III studies of treatment, and treatment decisions must be determined from single-institution reports and retrospective studies. Since the end of the 1980s, whole body CT scan evaluation has become routine. The use of PET-CT in the initial staging of seminoma is still controversial[7]; however, its implementation in follow-up and decision-making in post-chemo or radiotherapy residual masses has been successfully proved.[8]

The issue of optimal radiation dose, total as well as daily dose, remains controversial.[9,10] A German Prospective Multicenter Clinical Trial[4] which enrolled 30 participating centers and 66 Stage IIA patients found that 30 Gy yielded 100% in-field tumor control and compared favorably with total doses (30–35 Gy, including boost) of previous reports in the literature[2,3,6] and also with the current literature.[1,11] It seems that only prospective studies, like the German Study, could reveal the most appropriate dose/schedule for IIA patients.

Acute and late side effects were low in our series. Leading pronounced problems in the past were severe gastrointestinal symptoms when abdominal fields with total doses between 3000 and 4000 cGy were used. Only two patients developed peptic ulcer disease and radiation-induced proctitis, cured totally with conservative treatment. In their 2012 study, Hallemeier et al.[11] also reported a very infrequent acute and late toxicity.

All but four of our patients were treated with the "hockey-stick" field covering only para-aortic and ipsilateral common iliac lymphatics. Our recent and others' experience[1,4] has

proved that limitation of the target volume can reduce absolutely side effects such as gastrointestinal, bony and second cancers, as well as reduce scatter dose to the contralateral testis. Using clinical, anatomic landmarks and nodal/vascular mapping, Wilder et al.[3] support placement of the superior border of all radiotherapy fields at T11/T12 and the inferior border at the top of the acetabulum. An antero-posterior–postero-anterior boost is delivered to the involved adenopathy with a 2 cm margin. Wilder et al.[3] suggested that cranial reduction of the superior border reduces the rate of cardiovascular and pulmonary late side effects, and delivers a smaller dose to the kidneys, stomach and bowel, with a reduced risk of second malignancies with no increased rates of relapse. Large studies have been done with the superior border at the top of the T11 vertebral body and even at T9/T10.[1,10] Whole pelvis should be considered only if lymphatic disruptions occur such as following pelvic operation, inguinal hernia repair or surgery due to mal- or undescended testis.[4,12] Prophylactic mediastinal and left supra-clavicular irradiation has been totally omitted due to its non-contribution to survival and increased rate of secondary malignancies, such as lung and thyroid cancer, and of cardiovascular diseases.[3,5]

Among the current radiotherapy strategies to improve the therapeutic ratio in early stage seminoma are computed tomography-based traditional radiotherapy, bone-marrow-sparing intensity modulated radiotherapy (BMS-IMRT), reducing the dose to the small and large bowel, stomach, pancreas and liver, and proton therapy.[13–15] Proton therapy was able to reduce acute and late treatment morbidity and improve therapeutic ratio through the "spread-out Bragg peak" phenomenon.[14] Proton treatment reduced the mean dose to abdominal and pelvic organs compared to 3-dimensional conformal radiotherapy (3-DCRT) and IMRT with a resultant more favorable dose distribution with less risk to out-of-field radiation-induced malignancies.[15] However, additional studies are warranted to assess the clinical benefit/disadvantage of these techniques.

Three patients developed late side effects of radiation therapy (Table 2). Because of the clear anatomic location of the 2nd and 3rd part of duodenum in the high-dose volume of the para-aortic field, peptic ulcer is the most common side-effect. Gunnlaugsson et al.[16] reported a strong correlation between the amount of small bowel irradiated to doses larger than 15 Gy and gastrointestinal side effects. Bamberg et al.[17] found acute gastrointestinal side effects more prevalent in irradiated Stage II compared to irradiated Stage I patients that could be attributed to the additional boost or to larger total doses used in the past. It is clear that dose reduction should translate into lower rates of acute and chronic side-effects. Efstathiou and Logothetis[18] emphasized the risk factors for the increased incidence of second malignancies, such as high radiation dose, young age at diagnosis, extended survival, and long follow-up.

Only one case of radiation-induced carcinoma was described (Table 2, patient 1). The patient was treated in 2002 with the "inverted-Y" method amounting to a dose of 3000 cGy, with 600 cGy additional boost. Due to the exposure of the pancreatic body and the stomach within the high-dose volume, such tumors have been described, albeit with doses higher than 3000 cGy.[19] The median age of our irradiated seminoma patients was 36 years (as was this patient), and their cumulative dose risk of developing solid cancers was 31% compared to 23% in the general population. The overall relative risk of radiation-induced second cancers in seminoma patients is approximately 2 after 10 years,[20] comparable to the relative risk of chemotherapy which is 1.8, especially when more than 4 cycles are given.[19] If combined modality is given, the relative risk is even higher.[2,9] Pathologically, the pattern of increasing risk of radiation-induced SPC suggests a direct radiogenic effect, and Zilli et al.[13] suggested contributing factors, such as scatter dose, number of monitor units, and volume of normal tissues receiving low-dose radiation.

5. Conclusion

Comparing important current studies to our own experience, we suggest that Stage IIA seminoma patients should be treated with a total dose of about 3000 cGy, including the boost. Regular CT scan or PET-CT should be implemented in the follow-up of these patients. Given the young age of our patients, patients probably remain at risk for late sequelae for the remainder of their lives and we recommend follow-up for life.

Conflict of interest

None declared.

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