Fertility After Adjuvant External Beam Radiotherapy For Stage I Seminoma

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Citation

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Abstract

Introduction: “Hockey stick” irradiation is the classical adjuvant treatment for patients with stage I testicular seminoma after orchiectomy, resulting in 98-99% long-term disease free survival. This treatment option has been recently challenged by two alternative approaches a) observation only or b) adjuvant chemotherapy. One of the concerns raised against radiotherapy has been an increased risk of infertility. Impaired spermatogenesis due to scattered and transmitted irradiation to the remaining testicle has been reported in several studies. Although recovery of sperm cell production is observed in most patients, long term oligospermia or azospermia remains an important concern in these mostly young patients.

Patients / Methods: We conducted a retrospective study addressing the question of paternity post “hockey stick” irradiation. We reviewed the medical records of 36 patients with stage I seminoma who received post-orchiectomy irradiation at Hadassah University Hospital between January 1994 and September 2004. Patients were contacted by telephone and interviewed regarding paternity status, fertility problems and any need for assisted reproduction treatments.

Results: All patients were treated on a high energy linear accelerator with “hockey stick” field to a dose of 22.5-24 Gy in 1.5 Gy fractions with an AP-PA technique. A testicular shell was always used. Semen preservation was recommended to all patients. With a median follow up of 88 months, no patient developed disease recurrence and the only second primary tumor observed was one contralateral testicular germ cell tumor. 13 of the 36 patients were older than 40 years of age and had children at the time of diagnosis, and did not attempt to have further children. One patient was known to be oligospermic and one was azospermic prior to diagnosis. 5 patients were lost to follow-up. Of the 15 patients left, 5 have not yet "tested" their fertility. The 10 who have tried to conceive succeeded with no need for any interventions. 5 of them have each 2 children born after treatment, the other 5 have each one child. The patient with oligospermia had a successful IVF.

Conclusions: In our experience, patients treated with adjuvant post-orchiectomy “hockey stick” radiotherapy preserved their fertility. None of those who wanted to reproduce needed any intervention.

NOTE

Dr. Mark Wygoda is an equal contributor to the manuscript

INTRODUCTION

Seminoma is the most common testicular tumor among young men between the ages of 25 and 35 years. Disease occurs during the peak age of reproductive life and at a key time for the patient and family. Infradiaphrgmatic radiotherapy represents a safe and easily applicable adjuvant treatment with a 99% long-term survival. ([1]) This has led to an increased interest in the quality of life and late sequelae of these long-term cancer survivors. Treatment-induced involuntary infertility is a major concern in cured cancer patients. For example, prior to their treatment 88% of testicular cancer patients did not exclude future paternity ([2]).

Testicular cancer is the only malignancy where there is evidence of a common etiology for the malignant process and reduced fertility. Subfertility or infertility can be associated with the testicular disease itself or with its treatment. Prior diagnosis of infertility is associated with a 2-10 fold increased risk of testicular cancer. ([3]) About half of testicular cancer patients suffer from defective spermatogenesis before any treatment interventions are undertaken ([4],[5]).

“Hockey stick” irradiation is the classical adjuvant treatment

for patients with stage I testicular seminoma after orchiectomy, resulting in 98-99% long-term disease free survival. This treatment option has been challenged by two alternative approaches a) observation only or b) adjuvant chemotherapy. Relapses at 5 years are reported after adjuvant radiotherapy

in 2%–3% of the patients with Stage I seminoma ([6,7]), but occur in 20% of the patients who undergo a surveillance strategy and are usually localized to the para-aortic nodes ([8]).

One of the concerns raised against radiotherapy has been an increased risk of infertility. Impaired spermatogenesis due to scattered and transmitted irradiation to the remaining testicle has been reported in several studies. After inhibition of spermatogenesis for 6–8 months, spermatogenesis is generally recovered after 1–2 years, but might be incomplete or take a longer time in some patients. Repair of sperm-cell production is more rapid and complete in younger patients and patients with normal pretreatment sperm quality. ([9])

Huyghe et al. analyzed the impact of testicular cancer (TC) treatment on fertility in 451 France patients and observed the fertility rate in patients with TC decreased by roughly 30% after treatment and radiotherapy appeared to have a more deleterious effect on fertility when compared with chemotherapy ([10])

Brydøy et al, however, have reported comparable post-treatment paternity rates in testicular cancer patients treated by retroperitoneal lymph node dissection, radiotherapy, and low-dose chemotherapy. ([11])

We investigated paternity in 36 patients after “hockey stick” irradiation for stage I seminoma by conducting a retrospective study.

PATIENTS AND METHODS

PATIENT SELECTION AND STAGING PROCESS

Clinical data and treatment modalities were retrospectively reviewed for 36 patients with stage I pure seminoma seen at our institution between January 1994 and September 2004. All patients had under-gone an inguinal orchiectomy and were referred to the department of radiation oncology for radiotherapy.

After orchiectomy, all cases were staged as I according to the TNM staging system ([12]) on the basis of normal clinical examination, chest and abdominal CT scan findings, either normal or falling beta-HCG (three patients) following orchiectomy in accordance with the expected half-live for beta-HCG.

RADIOTHERAPY

All 36 patients underwent post-orchiectomy irradiation with “hockey stick” field in the Radiation Oncology Department of Hadassah University Hospital. Semen preservation was recommended to all patients. Radiotherapy was applied through anterior-posterior opposing fields with 6–18 MV photons of linear accelerators. Both opposing fields were treated daily for five times a week with a fraction of 1.5 Gy daily as specified in the ICRU 29 report for opposing fields. A total dose of 22.5-24 Gy was applied in 15-16 days.

Margins of the treatment portals were defined according to the following criteria: upper field border, the disk between T10 and T11; lower field border, the mid-obturator foramen; the ipsilateral field margin, renal hilum down to the disk between the L5 and S1, then to the lateral edge of the acetabulum and vertically downward to the mid-obturator level; the contralateral margin included the transverse process down to L5–S1, then diagonally in parallel to the ipsilateral margin and then vertically to the median border of the obturator foramen. A testicular shielding shell was always used.

FOLLOW-UP

Follow-up was conducted by chart review, by writing to and/or calling the patients. Patients were contacted by telephone and interviewed regarding paternity status (number of children, pregnancies achieved naturally or through in vitro fertilization methods), fertility problems, the time required by the couple to achieve conception and any need for assisted reproduction treatments.

RESULTS

TREATMENT OUTCOME

Median age of the patients was 34.5 years (range 18-63 years).

The median follow up period was 88 months (range 12-132 months). 5 patients were lost to follow-up.

Of the 31 invited men, no patient developed in field recurrence or distant metastases. One patient developed contralateral testicular cancer, he was treated by orchiectomy only and was subsequently disease free.

PATERNITY

13 of the 36 patients were older than 40 years and had

children at the time of diagnosis, and did not attempt to have further children. 1 patient was known to be oligospermic and one was azospermic prior to diagnosis. 5 patients were lost to follow-up. Of the 15 patients left, 5 have not yet tried to father a child. The 10 who have tried to conceive succeeded with no need for any interventions. 5 of them have each 2 children born after treatment and the other 5 have each one child. One patient with oligospermia had a successful IVF.

DISCUSSION

In the present series, adjuvant post-orchiectomy "hockey stick" radiotherapy showed high efficacy in stage I seminoma with minimal acute toxicity and no significant side effects. We have not shown any significant impairment of fertility after adjuvant "hockey stick" radiotherapy. All 10 patients, who have tried to conceive, succeeded with no need for any interventions.

Post-orchiectomy external-beam radiotherapy has been the treatment of choice in patients with seminoma stage I for decades. The target volume has traditionally covered the bilateral para-aortic and the ipsilateral ileac lymph nodes.

Studies on the effects of adjuvant radiotherapy on the long-term fertility of patients with stage I seminoma are of special interest because about 80% of them are over treated. ([8])

Brydoy et al established that the long-term paternity rate for patients who underwent radiotherapy for testicular cancer is significantly lower than for patients followed by surveillance. In cohort 554 Norwegian men treated for testicular cancer 15-year actuarial post-treatment paternity rate was 81%, 65% and 62% in the surveillance group, radiotherapy and chemotherapy groups respectively. ([11]) However, this has not been confirmed by Huddart, who studied gonadal function and paternity in 680 British men treated for testicular cancer. In a cohort of 32 patients who had tried to father a child following radiotherapy, 28 (82%) had succeeded in fathering biological children, compared 56 of 66 (85%) in the surveillance group. ([13])

Huyghe et al. found radiotherapy to be more deleterious to subsequent fertility than chemotherapy in patients with testicular cancer, ([10]) but this has not been confirmed by other groups ([11],[13])

Special techniques for gonadal shielding reduce the scattered radiation dose to the contralateral testicle to approximately 0.3-0.5 Gy. Infradiaphragmatic radiotherapy, restricted to the para-aortic field, can decrease the median testicular radiation dose as low as 0.1 Gy, with no reduction in sperm counts 1 year after irradiation. ([14]) United Kingdom phase III trial compared para-aortic field irradiation with conventional "hockey stick" irradiation. Para aortic irradiation was associated with lower acute gastrointestinal, hematologic and gonadal toxicity and similar relapse free survival and overall survival compared to "hockey stick" irradiation. ([1]) Several studies suggest similar efficacy and much lower toxicity of a target dose of 20 Gy compared with a target dose 30Gy. ([15],[16])

In recent years the use of single-agent carboplatin has shown promising results. One injection of carboplatin at a dose of AUC×7 has shown to be an effective adjuvant treatment for stage I seminoma and similar in outcome to recent radiotherapy schedules. Carboplatin has fewer acute toxic effects than radiotherapy, and possibly reduces the incidence of contralateral second germ-cell tumours. However, these findings need to be confirmed beyond 4 years of follow-up. ([17])

Cryopreservation of semen should today be offered to all young men starting radiotherapy or chemotherapy for a testicular cancer, even in those who are highly oligospermic. Although only 10–20% of patients finally use their deep-frozen semen, ([9]) the discussion of post-treatment fertility with a newly diagnosed young cancer patient creates hope in a stressful situation when he faces a life-threatening disease.

Conclusion: In our experience, patients treated with adjuvant post-orchiectomy "hockey stick" radiotherapy preserved their fertility. None of those who wanted to reproduce needed assisted reproduction treatments. Nevertheless, long-term effects of radiotherapy, methods to preserve fertility and alternative strategies should be discussed before initiation of treatment

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