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Original Article

Current Practice Patterns Surrounding Fertility Concerns in Stage I Seminoma Patients: Survey of United States Radiation Oncologists

Carl M. Post, BS,[1] Aditya Jain,[2,3] Catherine Degnin, MS,[3] Yiyi Chen, PhD,[3] Mike Craycraft, RPh,[4] Arthur Y. Hung, MD,[3] Jerry J. Jaboin, MD, PhD,[3] Charles R. Thomas Jr., MD,[3] and Timur Mitin, MD, PhD[3]

Purpose: Patients with testicular seminoma may face fertility issues because of their underlying disease as well as treatments they undergo. The current patterns of practice among U.S. radiation oncologists aimed at assessing and preserving fertility in patients with Stage I seminoma are unknown.
Methods: We surveyed practicing U.S. radiation oncologists via an Institutional Review Board-approved online questionnaire. Respondents' characteristics and perceived patient infertility rates were analyzed for association with treatment recommendations.
Results: We received 353 responses, of whom one quarter (23%) consider themselves experts. A vast majority (84%) recommend observation as a default strategy. Fifty-two percent routinely advise fertility assessment for patients before observation or chemotherapy, and 74% routinely do so before adjuvant radiation therapy (RT). Forty-one percent and 43% believe that 10% and 30% of patients are infertile following orchiectomy, respectively. Thirty-seven percent and 22% believe infertility rates following para-aortic RT to be 30% and 50%, respectively. Eighty percent routinely use clamshell scrotal shielding. Responders with higher perceived infertility rates are more likely to recommend fertility assessment/sperm banking (Fisher's exact $p < 0.0001$). Responders who routinely advised fertility assessment were more likely to use clamshell shielding (Cochran–Armitage trend test $p = 0.0007$). Clamshell use was positively correlated with higher perceived infertility rates following para-aortic RT (Spearman's correlation coefficient = 0.006).
Conclusions: Despite a clear knowledge of fertility issues in men diagnosed with seminoma, there is no universal adoption of fertility assessment among U.S. radiation oncologists.

Keywords: testicular seminoma, adjuvant therapy, radiation therapy, fertility, patterns of care, survey

Introduction

Testicular germ cell tumors (GCTs) comprise only 1% of all male tumors, however, the incidence continues to rise in the younger population, making them the most common solid tumors in men aged 20–34 years old.[1,2] Seminomas constitute the majority of GCTs, with over three-quarters diagnosed as Stage I.[3] Radical orchiectomy alone achieves excellent cure rates of 80%, with cancer-specific survival rates >99% regardless if observation, adjuvant, or salvage therapy with radiation (RT) or chemotherapy is needed.[4–7] Consequently, NCCN guidelines recommend active surveillance in this patient population, with additional treatment reserved for cases of relapse.[8] National practice patterns have responded accordingly, with observation occurring in 60% of cases, and RT rates approaching 20%, as opposed to 80% before the 21st century.[6,9,10]

The transition away from adjuvant RT toward observation is a true victory for evidence-based medicine, as it does not jeopardize outcomes and avoids the associated side effects of adjuvant therapies. Nevertheless, the associated risks of impaired fertility, hypogonadism, cardiovascular disease, and secondary malignancy are major toxicities that need to be addressed and minimized if adjuvant RT is considered.[3] In

[1]Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, Nebraska.
[2]Boston University, Boston, Massachusetts.
[3]Department of Radiation Medicine, Oregon Health and Science University, Portland, Oregon.
[4]Testicular Cancer Society, Cincinnati, Ohio.

regard to fertility, it has been shown that even before orchiectomy, seminoma patients have significantly lower sperm counts compared with controls, with the median classified with mild oligospermia (15×10^6/mL).[11] A 2001 study showed that following orchiectomy nearly half of patients were oligospermic or azoospermic, with 75% returning to normospermia after 1 year.[12] The effect of RT on fertility is also influenced by the target volume. Inclusion of the ipsilateral iliac lymph nodes in addition to the para-aortic lymph nodes (''dog-leg'' field) has higher mean radiation dose to the contralateral testicle compared to para-aortic strip RT alone, and this amount is further reduced with the use of a testicular clamshell shield.[13]

Despite baseline subfertility in this population, paternity rates are still high at 71% at 15 years, although the ability to conceive and time to conception are negatively impacted with any adjuvant treatment, most notably with high-dose chemotherapy.[14] Semen cryopreservation use has increased in response to the fertility issues made worse with treatment, as nearly half of patients undergo sperm banking if offered.[15] Not surprisingly, the NCCN recommends offering semen analysis and sperm banking information before adjuvant therapy, as well as the routine use of clamshell shielding during RT in all patients. The current adherence to these national guidelines is unclear as the two most recent retrospective national data base analyses in 2012–2013 (RT rate of 20%) conflicted with practice patterns tabulated from a survey in the same year (RT rate of 62%).[6,9,16]

Thus, using an anonymous electronic survey of practicing U.S. radiation oncologists, we set out to examine the most contemporary patterns of practice. We hypothesized that U.S. radiation oncologists would have embraced observation as the first choice option for these patients, and we wanted to determine if steps are being taken to address and minimize the side effects associated with adjuvant RT.

Materials and Methods

Survey instrument development

The study was approved by the Oregon Health and Science Institute (OHSU) Institutional Review Board. The online survey (Supplementary Fig. S1; Supplementary Data are available online at www.liebertpub.com/jayao) was developed using the Research Electronic Data Capture (REDCap) software, patented by Vanderbilt Medical Center, and licensed by the Oregon Clinical and Translational Research Institute (OCTRI) for use by OHSU. The survey was designed to be completed in less than 2 minutes. It was reviewed by a panel of resident and faculty physicians in our department, and all feedback was incorporated into the final survey. The survey contained 25 questions regarding respondent demographics and treatment recommendations/considerations for various clinical scenarios. Branching logic was used to tailor the questions based on previous responses, such that most respondents were not exposed to all 25 questions. Respondent characteristics included information regarding practice setting (academic or private), years since completion of residency, and geographical location. In addition, respondents self-rated their depth of knowledge in the field of testicular seminoma and were grouped into three categories–not comfortable with evaluating a patient with seminoma, comfortable with evaluating and treating, and expert-level knowledge of the field.

Data collection

The data sample was collected through a fully anonymous online survey of radiation oncologists in the United States. No incentives were offered to respondents, so as to maintain complete anonymity. Each participant was contacted and invited to complete the survey using the REDCap tool. The invitation contained instructions for participation, information regarding the study, and contact information. The first invitation was sent on September 8, 2016. Participants who requested not to be contacted in the future were immediately removed from the database. The remaining respondents were contacted with a reminder e-mail on September 18, 2016, to maximize response rate. No further communication with participants ensued.

Statistical analysis

Respondents were characterized by years since residency completion, number of testicular seminoma patients evaluated in the past year, number of testicular seminoma patients treated with radiotherapy in the past year, practice setting, geographic region of practice, and self-rated knowledge. These six factors were analyzed for correlation with respondent treatment recommendations. Pearson's chi-square test was used to examine the correlation between characteristics and treatment questions. When the sample size was small we used the Fisher's exact test instead. Cochran–Armitage test was used to assess trends in change of ordinal categorical values. A p value <0.05 was considered statistically significant. SAS 9.4 (Cary, NY) was used for statistical analysis.

Results

The survey was sent to 6967 e-mail addresses, some of which could belong to the same individuals, as the developed database used both personal and institutional e-mail addresses. We received 712 undeliverable/failed automatic responses, 74 nonapplicable/ineligible responses, and 353 completed responses, among which one was from a non-radiation oncologist, thus excluded from analysis. Characteristics of 352 radiation oncologists are summarized in Table 1.

Survey respondent demographics

Most respondents (>70%) completed residency training more than 10 years ago, most (73%) feel comfortable evaluating and treating patients with testicular seminoma, and 23% consider themselves experts in this field. Over 30% of respondents did not see any patients with testicular seminoma over the past year, and over 50% did not treat testicular seminoma with RT over the course of the year. Very few (<3%) treated more than five patients with testicular seminoma over the past 12 months.

Most respondents recommended fertility assessment and correctly identified baseline subfertility

Among respondents, over 80% of respondents assess the rate of infertility among patients undergoing orchiectomy between 10% and 30% (Fig. 1A, Table 2). Fifty-two percent of respondents always recommend fertility assessment if observation or chemotherapy are pursued. Twenty-five percent of

Table 1. Demographics of the Surveyed Population

	No. of respondents (%)
No. of years after completion of residency training	
Currently in residency training	10 (2.84)
0–2	15 (4.26)
3–5	26 (7.39)
6–10	48 (13.64)
Over 10	253 (71.88)
No. of testicular seminoma patients evaluated over the past 12 months	
0	112 (31.82)
<5	215 (60.08)
5–10	18 (5.11)
>10	7 (1.99)
No. of testicular seminoma patients treated with RT over the past 12 months	
0	187 (53.13)
<5	155 (44.03)
5–10	7 (1.99)
>10	3 (0.85)
Practice setting	
Academic center	127 (36.08)
Private practice	225 (63.92)
Practice region	
Northern	81 (23.01)
Pacific	62 (17.61)
Southern	70 (19.89)
Western	40 (11.36)
Central	85 (24.15)
Others/unknown	12 (3.41)
Canada	2 (0.57)
Self-assessed depth of knowledge in the field of testicular seminoma	
Not comfortable evaluating patients	13 (3.69)
Comfortable evaluating, but not an expert	257 (73.01)
Expert in this field	82 (23.30)

RT, radiation therapy.

respondents assess the rate of infertility among patients undergoing para-aortic RT after orchiectomy at 50% or higher, and 69% of respondents assess the rate of infertility after para-aortic RT between 10% and 30% (Fig. 1B). However, only 74% of respondents routinely offer to their patients undergoing para-aortic RT fertility assessment.

There is a strong association between perceived rate of infertility and recommending fertility assessment after orchiectomy both in the setting of para-aortic RT ($p<0.01$) and with no adjuvant RT ($p<0.01$).

Most respondents routinely use clamshell shielding and avoid dog-leg RT

Adjuvant RT considerations are shown in Table 3. Computed Tomography (CT) simulation is universally utilized by the surveyed radiation oncologists, and a majority (80.4%) includes the ipsilateral renal hilum in the target volume. Twenty-two percent routinely include the ipsilateral pelvic lymph nodes (dog-leg field) in addition to the para-aortics. More than 70% routinely use clamshell shielding with

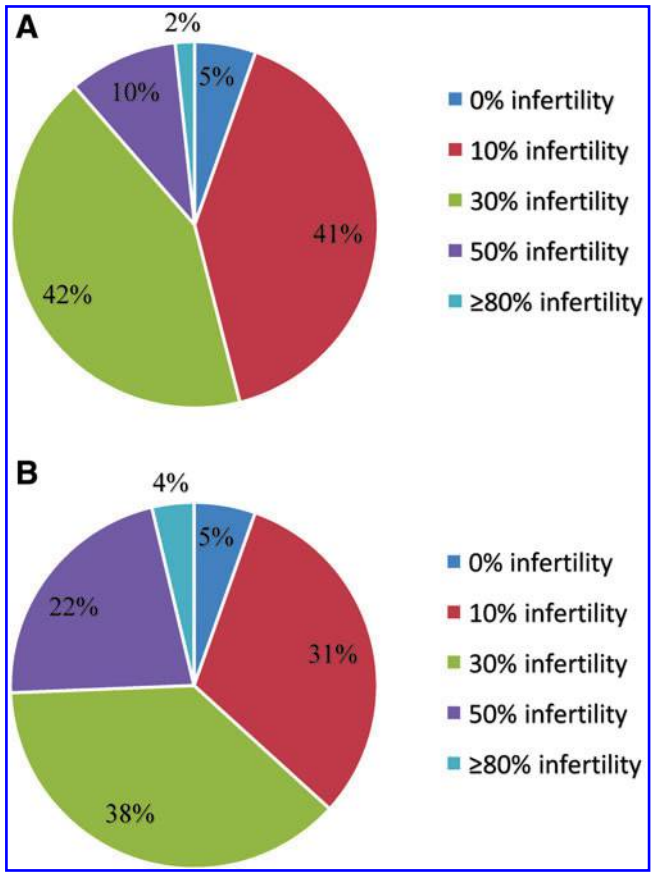

FIG. 1. Respondent estimation of infertility after orchiectomy **(A)** and para-aortic radiation therapy **(B)**. Color images available online at www.liebertpub.com/jayao

treatment. The most common treatment fractionation schemes used by respondents are 25.5 Gy in 1.5 Gy fractions (50%) and 20 Gy in 2 Gy fractions (45%). Responders who routinely advise their patients to receive fertility assessment/sperm banking are more likely to use the clamshell for shielding during RT (Cochran–Armitage trend test $p=0.0007$). The frequency of clamshell use is correlated with the perceived infertility rate after para-aortic RT (Spearman's correlation coefficient $p=0.0006$).

History of pelvic surgery affects adjuvant treatment recommendation

For a patient with Stage I seminoma, 84% of respondents recommend observation following orchiectomy, while 10% recommend adjuvant RT, and 6% recommend adjuvant chemotherapy. However, 42% of respondents adjust their recommendations if their patient with Stage I seminoma had a prior history of pelvic surgery. Of those respondents who alter their recommendation, 41% recommend adjuvant chemotherapy, 41% recommend adjuvant radiation with dog-leg field, 10% recommend observation, and 7% recommend adjuvant RT with para-aortic field. Respondents with 0–2 or >10 years of professional experience since completion of residency training were less likely to alter their treatment recommendation based on the history of pelvic surgery, compared with respondents with 3–10 years of professional experience ($p=0.0032$).

Table 2. Practice Patterns Regarding Fertility

	No. of respondents (%)
Recommends fertility assessment/sperm banking if patient elects observation or chemotherapy	
Never	41 (11.65)
Sometimes	66 (18.75)
Often	62 (17.61)
Always	183 (51.99)
Recommends fertility assessment/sperm banking if patient elects RT	
Never	11 (3.13)
Sometimes	32 (9.09)
Often	47 (13.35)
Always	262 (74.43)
Estimated percent of patients that are infertile after orchiectomy for testicular seminoma	
0%	19 (5.4)
10%	143 (40.63)
30%	150 (42.61)
50%	34 (9.66)
$\geq$80%	6 (1.70)
Estimated percent of patients who are infertile after para-aortic RT	
0%	19 (5.41)
10%	110 (31.34)
30%	132 (37.61)
50%	77 (21.94)
$\geq$80%	13 (3.70)

Discussion

To our knowledge, this is the first survey of practicing U.S. radiation oncologists who focus on fertility issues in men with Stage I seminoma who receive adjuvant therapy or are observed following definitive treatment. The response rate is difficult to estimate with this database, as multiple e-mail addresses may belong to the same physician; however, this response rate is similar to previously published surveys utilizing the same database.[17–22] Despite the low response rate, the high number of responses is a strength of this work, which allows us to draw well-supported conclusions about current practice patterns. Baseline subfertility is common in this patient population, and infertility rates in prior studies have been shown to approach 30% after orchiectomy.[14] Therefore, acute awareness of these issues and proper counseling of patients after orchiectomy are critical for all oncology providers.

Table 3. Adjuvant Radiation Therapy Considerations

	No. of respondents (%)
Routine use of CT simulation	
Yes	352 (100)
No	0 (0)
Routine inclusion of left renal hilum in left-sided tumors	
Yes	283 (80.4)
No	69 (19.6)
Routine inclusion of ipsilateral pelvic lymph nodes (dog-leg field)	
Yes	77 (21.88)
No	275 (78.13)
Routine use of clamshell scrotal shield	
Yes	259 (73.58)
No	93 (26.42)
Dosing/fractionation	
20 Gy in 2 Gy fractions	159 (45.17)
25.5 Gy in 1.5 Gy fractions	175 (49.72)
30 Gy in 2 Gy fractions	7 (1.99)
Other	11 (3.13)

CT, computed tomography.

Most respondents correctly identify baseline subfertility following surgery, however, fertility assessment is underutilized regardless of adjuvant treatment option pursued

Our surveyed physicians did not underestimate the infertility rates in seminoma patients. In 2002, M.D. Anderson conducted a survey of male cancer patients, whose fertility was potentially impacted by cancer treatment, to determine their attitudes and experiences regarding cancer-related infertility. Of the 201 respondents, only 60% recalled being told about the risk of infertility with treatment, 51% recalled education about sperm banking before treatment, and 24% chose to cryopreserve sperm before treatment. Forty-five percent of patients did not bank sperm because they either did not get any/enough information or they or their physician did not think that fertility would be compromised with therapy.[23]

Despite the awareness of our surveyed population, fertility assessment is not universal, as only 74% recommend semen analysis/sperm banking before adjuvant RT. Even fewer respondents (52%) advise patients to seek fertility assessment and sperm banking services if patients do not elect to proceed with adjuvant RT. This difference may or may not be explained by a perceived increase in the rate of infertility after adjuvant RT. It may also stem from radiation oncologist's perceived ownership of a patient's best interest only in those undergoing RT, whereas for patients who are observed or received chemotherapy, the onus on fertility assessment is believed to be on other involved medical providers.

Interestingly, some research has shown that sperm production/counts in seminoma patients may increase or remain stable after orchiectomy, which is reflected in observed higher rates of azoospermia before surgery.[24,25] Consequently, urologists are optimally positioned to address infertility and discuss fertility assessment with seminoma patients. A similar survey should be conducted among surgeons to bring light to this important topic, as the prevalence of these discussions is unknown. Regardless of surgeon practices and a history of fertility assessment, radiation oncologists should independently discuss fertility with patients during consultation. Despite the excellent oncologic outcomes for Stage I seminoma patients, this cancer remains a stressful diagnosis to patients due to fertility concerns.[23,26] Thus, fertility should be a key issue that is universally addressed by all treating physicians.

Strategies to minimize contralateral testis scatter radiation, including clamshell shielding and para-aortic strip RT, are not universally adopted

Adjuvant RT can affect fertility if the scattered dose to the remaining testicle is significant. Fifty cGy of testicular

irradiation produces transient and 100 cGy permanent azoospermia. Para-aortic RT, in comparison to a classic dog-leg RT with inclusion of ipsilateral pelvic lymphatic drainage, reduces the mean gonadal dose from 32 cGy to 9 cGy ($p < 0.001$).[27] Two large prospective trials have shown that para-aortic RT does not compromise oncologic outcomes in patients with Stage I seminoma.[28,29] If dog-leg field is pursued, scrotal shielding with a clamshell can dramatically decrease the scattered dose to the remaining testicle. Mean testicular doses in a 1999 study by Bieri et al. were 54.46 and 20.72 cGy for dog-leg RT without and with clamshell shielding, respectively.[13] Whether the use of a clamshell device with para-aortic irradiation leads to improvement in fertility preservation is not studied, however, the principle of ALARA (as low as reasonably achievable) is fundamental in applied radiation biology and we believe that it should always be followed clinically. A majority of respondents routinely cover only the para-aortic lymph nodes during RT (78%) and use clamshell shielding during treatment (74%), however, these practices were not universal. A limitation of this study is that the binary nature of surveys simplifies clinical reasoning, and the specific reasons clinicians have for recommending dog-leg RT and/or not using a clamshell are unknown.

Most respondents recommend observation for patients with Stage I testicular seminoma, but unfounded fears often lead to the pursuit of adjuvant treatment

Our surveyed population largely agrees (84%) that observation is the best management for patients with Stage I seminoma, however, it is clear that many patients still receive adjuvant treatment for various reasons. Our previous article indicates that adjuvant treatment is embraced by 97% of respondents when patients are perceived to be noncompliant with observation. As seen in this analysis, the transition away from observation is also commonly seen in patients with a history of pelvic surgery. Prior pelvic surgery has historically been perceived as a risk factor for pelvic recurrence of seminoma, secondary to altered lymphatic drainage, however, there has been no clear evidence to support this claim. A report by Klein et al. in 1984,[30] commenting on germ cell testicular tumor recurrences over a 34-year period, seems to be the foundation for this conclusion, which has influenced several studies.[29,31] Twenty-two recurrences (seminoma $n = 5$) were documented, 21 of which were in patients with prior pelvic surgery.

Despite very low rates of groin metastases overall, this research has had a broad impact, even enough to influence NCCN guidelines, which urge adjuvant chemotherapy instead of RT in patients with a prior pelvic surgery history.[2] The generalizability of the Klein study to Stage I seminoma patients must be questioned, especially in light of more recent evidence. A large Danish prospective study in 2006 of 695 patients (seminoma $n = 394$) with Stage I testicular cancer who were observed after orchiectomy showed an inguinal lymph node relapse rate of 2%, 84% of which had nonseminomatous tumors, and only one had a history of pelvic surgery. Furthermore, all the study patients with inguinal metastases were salvaged effectively with either chemotherapy or RT and had no evidence of disease at follow-up.[32] More education is necessary to dispel this fear of increased disease recurrence among physicians and patients, and empower patients not to fear disease recurrence due to highly effective treatment options available in the salvage setting.

Conclusions

Our survey of practicing radiation oncologists in the United States reveals a gap between knowledge of fertility issues in men diagnosed with Stage I testicular seminoma and frequency of patient education and fertility counseling. We also question the current patterns of altering treatment recommendations based on the history of pelvic surgery and the nonuniform adherence to the principle of ALARA with scrotal shielding utilization and avoidance of dog-leg RT.

Authors' Contributions

C.M.P. and T.M. contributed to writing and visualization of the original article. All authors contributed to the design and conceptualization of the project as well as editing of the article for intellectual content. All authors read and approved the final article.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Timur Mitin, MD, PhD
Department of Radiation Medicine
Oregon Health and Science University
Portland, OR 97239

Email: mitin@ohsu.edu