Prospective phase I study on testicular castration induced by radiation treatment

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Introduction: *Surgery and luteinizing hormone-releasing hormone (LHRH) analogs are standard androgen deprivation treatments (ADT) for patients with advanced prostate cancer. We performed a phase I study to explore if irradiation to the testes could be used as an alternative to ADT.*

Materials and methods: *All patients had advanced prostate cancer with normal testosterone levels before treatment and indication for long term castration. Treatment started with one LHRH analog injection (to induce a fast drop of testosterone) followed by irradiation to the whole scrotum. Two fractionation regimens were tested: 17 Gy in 2 fractions, and 24 Gy in 3 fractions. Hormonal blood evaluation was performed before and every 3 months after radiotherapy. Toxicity was evaluated at each visit by the CTCv3 scoring system. This was an IRB approved prospective study.*

Results: *The first three patients received 17 Gy in 2 fractions. None of them developed acute or late skin toxicity and none became castrated, keeping normal levels of testosterone during the time they were followed at 11, 24 and 36 months post-radiotherapy. Another four patients received 24 Gy in 3 fractions. Two developed grade 1 temporary acute dermatitis and, again, none of them became castrated during follow up of 11-36 months.*

Conclusions: *Prospective studies assessing the effect of the Leydig cells after direct irradiation to the testes are rare. The two radiotherapy regimens used in this study were well tolerated, but not capable of causing castration after 11-36 months of follow up. It is not yet clear whether radiation treatment can effectively induce castration in men.*

Key Words: radiotherapy, castration, prostate cancer

Introduction

Androgen deprivation therapy (ADT) leads to objective responses and/or normalizes serum prostate-specific antigen (PSA) in over 90% of patients with prostate cancer.[1] The testes account for 90%-95% of total circulating testosterone, while the adrenal glands produce the remainder. Bilateral orchiectomy was the standard by which other forms of hormone therapy were measured in patients with prostate cancer.[2] Following orchiectomy, serum testosterone quickly falls to castrate levels.[3] However, despite its proven efficacy, there has been a dramatic decline in the utilization of bilateral orchiectomy. Reasons include the availability of luteinizing hormone-releasing hormone (LHRH) analog compounds and the negative psychological impact of orchiectomy on patients.[4]

Randomized trials comparing LHRH analog therapy to orchiectomy have shown equivalent efficacy.[5] Although the two different approaches to ADT (surgery and LHRH analog therapy) have similar effects on survival and quality of life, costs vary substantially when comparing the one-time expense of orchiectomy versus ongoing treatment with LHRH analog therapy.[6]

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Based on the above information, we began a phase 1 study using direct irradiation to the testes as an alternative to ADT. Gonads are known to be radiosensitive.[7] Radiotherapy to the gonads is relatively easy to deliver and has also the advantage of keeping the testes in the scrotum.

The objectives of the study were to evaluate the castration effectiveness and tolerance after two different regimens of external beam radiotherapy to the testes. This paper reports the results of that experience.

Materials and methods

Locally advanced prostate cancer patients with indication of long term ADT and who accepted permanent castration were eligible for this study. They should not be on ADT and should have a normal testosterone level before treatment. All patients received one injection of LHRH analog before the irradiation to the testes to guarantee immediate castration. Radiotherapy to the testes was given 2-3 weeks after the LHRH injection.

Skin (scrotal) toxicity was evaluated at each visit by the CTCv3 scoring system. The hormonal effect of irradiation on the testes was assessed by measurements of serum levels of testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol performed prior to treatment and every 3-4 months for the first 2 years and every 6 months thereafter. This was an IRB approved study and all patients signed an informed consent.

Treatment plan

After the initial LHRH analog therapy, a direct radiotherapy field with 6 MV energy was used to deliver the irradiation. A 5 mm bolus was applied over the scrotum and the dose was prescribed to a mid-testicular reference point as used by Classen et al,[8] Figure 1. Following irradiation, patients were assessed for toxicity and castration-response. LHRH hormonal therapy would resume only if castration was not achieved after the radiotherapy (defined by testosterone recovery within normal levels).

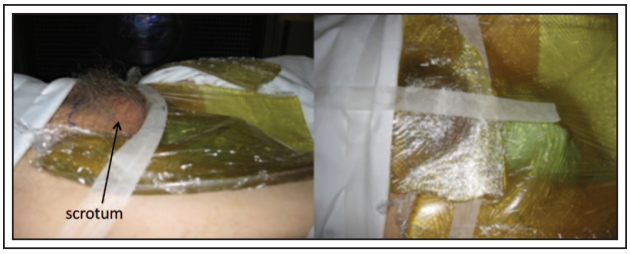

Figure 1. Illustration of one patient prepared to receive direct field of radiotherapy without (left) and with the 5 mm bolus over the scrotum.

TABLE 1. **Comparison between few common fractionation regimens with standard 2 Gy/day fractionation according to the linear quadratic formula (alpha/beta = 3 Gy).**

	2 Gy/day dose
20 Gy/5	28 Gy
17 Gy/2	39 Gy
24 Gy/3	53 Gy
30 Gy/10	36 Gy

Choice of the dose

This is a phase 1, dose-escalation study. Radiotherapy to the ovary at the dose of 20 Gy in 5 fractions was shown to be effective for ovarian castration in breast cancer.[9] Furthermore, impaired testicular function has already been described in patients receiving direct 20 Gy in 10 fractions of 2 Gy to both testes with the purpose of controlling testicular carcinoma in-situ.[10] Thus, arbitrarily, two regimens were designed to be tested sequentially: 1) 17 Gy in 2 fractions (given on days 1 and 7), and 2) 24 Gy in 3 fractions (on days 1, 7 and 21). Compared to a standard fractionation of 2 Gy per day these two regimens are equivalent to 39 Gy and 53 Gy, respectively. Table 1 compares few radiotherapy regimens with standard 2 Gy/day fractionation with alpha-beta = 3 Gy traditionally used for normal tissues.[7] Three patients were to be treated at the first dose level and observed for the castration and toxicity end-points as a classical phase I study. After 12 months post-radiotherapy to the scrotum, if castration levels of testosterone were not reached and treatment-tolerance was acceptable, a second group of patients would receive the second dose level and be assessed in a similar fashion. Unacceptable toxicity was defined as any treatment-related toxicity grade > 2.

Results

Starting in 2009, the first three patients entered the study and received 17 Gy in 2 fractions. None of them developed acute or late skin toxicity. None of them became castrated, always recovering normal levels of testosterone during the time they were followed. All three patients required further hormonal therapy after RT to the scrotum due to testosterone recovery to

TABLE 2. **Summary of the cases of the group that received 17 Gy in 2 fractions**

	Group 17 Gy in 2 fractions				Testosterone levels (normal: 2.8-21.6 nmol/L)	
Patient	**Age**	**Reason for ADT**	**Follow up time**	**Date scrotal RT (months)**	**Pre-treatment nmol/L**	**Examples of testosterone levels post-RT (date)**
1	67	Biochemical failure	24	5/Nov/09	30.4	4.9 nmol/L (29/Oct/10)
2*	52	Mestastases*	11	4/Nov/09	8.0	4.6 nmol/L (01/Sep/10)
3	65	High risk disease	36	25/Aug/10	6.3	5.1 nmol/L (21/Feb/12)

*this patient died after 11 months of follow up
ADT = androgen depletion therapy; RT = radiotherapy

normal levels after the end of the effect of the LHRH analog injection. They were followed for 11, 24 and 36 months post-radiotherapy, respectively. Table 2 shows some characteristics of these patients.

Once it was revealed that 17 Gy/2 fractions did not induce castration after 1 year post-scrotal irradiation, another four patients entered the study in 2011 and received 24 Gy/3 fractions. Table 3 shows some characteristics of these patients. Two developed grade 1 dermatitis for 2-3 weeks. They were followed between 18-36 months and, again, none became castrated during the period of follow up. All four patients also required further hormonal therapy after the scrotal irradiation, having always the testosterone recovering to normal levels at the end of the effect of each LHRH analog injection.

The levels of LH and FSH followed the trend of testosterone as illustrated in Figure 2, dropping right after the LHRH analog was given, but returning to normal values after the end of the effect of the LHRH analog medication.

Discussion

The germ cells responsible for the exocrine function of the testis (production of spermatozoids) are known to be very radiosensitive. Direct irradiation to the testes, with dose as low as 0.15 Gy causes significant depression in the sperm count; temporary azoospermia occurs after a dose of only 0.3 Gy.[11] The cells responsible for the endocrine function (Leydig cells) are more resistant than the germ cells and need higher

TABLE 3. **Summary of the cases of the group that received 24 Gy in 3 fractions**

	Group 24 Gy in 3 fractions				Testosterone levels (normal: 2.8-21.6 nmol/L)	
Patient	**Age**	**Reason for ADT**	**Follow up time**	**Date scrotal RT (months)**	**Pre-treatment nmol/L**	**Examples of testosterone levels post-RT (date)**
1	70	High risk disease	24	24/May/11	8.2	5.2 nmol/L (26/Sep/12)
2	78	High risk disease	18	22/June/11	5.8	6.6 nmol/L (29/Feb/12)
3	71	High risk disease	30	02/Aug/11	7.4	5.1 nmol/L (31/Dec/12)
4	63	High risk disease	18	26/July/11	14.8	5.9 nmol/L (26/Nov/12)

doses of radiation to express damage, as reported in retrospective studies.[11,12]

There is little prospective data on the effect of the endocrine function after ionizing irradiation to the testes. Since 1991, a group from Denmark has been studying the potential effect of radiotherapy on the testicular function following doses of 14 Gy to 20 Gy, in fractions of 2 Gy per day, given with the purpose of controlling carcinoma in-situ of the testes but attempting to preserve the endocrine function.[10] The authors report a decrease of basic total serum testosterone level, seen after median 3.2 months post-radiotherapy, as compared with the pre-irradiation values. However, the testosterone levels were always within normal values ranging from 11.6 nmol/L to 12.2 nmol/L, not even close to castration levels. In our study, we did the opposite. We gave fewer, higher dose fractions attempting to rapidly obtain a castrate level of testosterone without significant skin toxicity. Our initial fractionation regimen of 17 Gy/2 fractions, theoretically equivalent to 39 Gy given with 2 Gy per day fraction, did not lead to castration after a range of 11-36 months of follow up. The second regimen of 24 Gy in 3 fractions, equivalent to 53 Gy with standard fractionation, also did not castrate any of the patients after a range of 18-36 months post-radiotherpay to the scrotum. It is conceivable that a longer follow up could show significant damage to the Leydig cells, enough to cause a castrated status. However, even if it this would be the case, this prolonged delay would not be useful for the purpose of a therapeutic radiation-induced castration in prostate cancer patients with advanced disease.

A major difference between the Danish experience and our study is that our patients received one injection of LHRH analog before the irradiation. That treatment could have changed the sensitivity of the Leydig cells to the radiotherapy. It has been reported that treatment

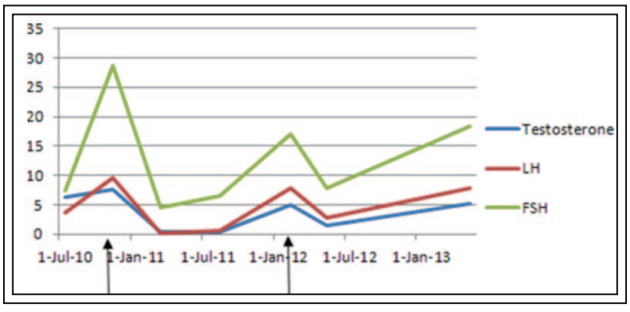

Figure 2. Illustrative curves showing blood level of FSH, LH and testosterone of one patient. Arrows represent hormonal LHRH analog injections.

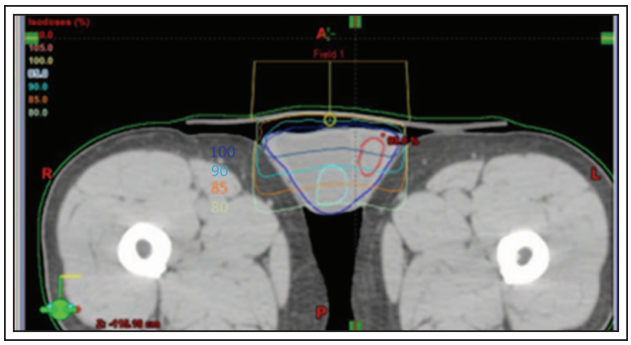

Figure 3. CT scan of a patient showing the isodose distribution to the scrotum with a direct 6 MV field.

with LHRH analogs reduces the testicular Leydig cell counts.[13]

After irradiation alone to the testes, LH and FSH tend to increase,[14] but in our study, LH and FSH decreased (following the testosterone level) in all cases, probably due to the pre-radiotherapy hormonal treatment, Figure 2.

It seems that there is a greater vulnerability to radiation-induced damage to Leydig cells in younger people compared to older adult males.[15] Our patients were older than the patients treated for carcinoma in-situ reported in the Danish study.[10] This age difference could perhaps explain the apparent more resistance of the Leydig cells after the irradiation in our group of patients.

It is worth pointing out that there is better ways to deliver appropriate doses of irradiation to the testes than with a direct field. One of our patients had a planning CT scan performed just to give us a more precise idea of the real dose received by each testis. As shown in Figure 3, in that case one testis received 100%, but the other received 85% of the prescribed dose.

This investigation is limited by the small number of patients studied and by the use of a LHRH analog prior to radiotherapy. Despite these possible shortcomings, it is the first prospective study examining the potential role radiotherapy might have in ablating testosterone production by the testis. It suggests that the testicular endocrine function may be more resistant to radiotherapy than originally thought.

Conclusion

Prospective studies assessing Leydig cells' physiological function after direct irradiation to the testes are rare. The two radiotherapy regimens used in this present study were well tolerated, but not capable of causing definitive testosterone ablation, at least during the

11-36 months of follow up in men who received one LHRH analog injection just before the irradiation of both testes. It is not yet clear whether any appropriate radiotherapy regimen would be able to effectively induce castration in men. □

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