Practical management issues in bilateral testicular cancer

B.J.R. BARRASS, R. JONES*, J.D. GRAHAM and R.A. PERSAD
*Bristol Royal Infirmary, Bristol, and *University Hospital of North Staffordshire, Staffs, UK*

Accepted for publication 27 October 2003

INTRODUCTION

Testicular cancer is the commonest solid tumour among young men and 5% of them develop bilateral disease [1,2]. However, urologists encounter patients with bilateral testicular tumours relatively infrequently and such tumours present some unique problems which require careful management. This review aims to cover these issues in the light of the recent National Institute of Clinical Excellence (NICE) manual on the management of urological cancers [1].

RISK MODIFICATION AND SCREENING FOR BILATERAL TESTICULAR CANCER

Should testicular intra-epithelial neoplasia (TIN) be treated to prevent a second testicular tumour? TIN is generally accepted to be the universal precursor for all testicular germ cell tumours [3] and is found in the contralateral testis of ≈5% of patients undergoing radical orchidectomy [4]. This percentage is similar to the proportion of patients who develop a second testicular cancer [1,2], so patients destined to develop a second tumour can be identified by searching for TIN. Indeed, TIN can be detected on biopsy with a false-negative rate of 0.3% [5] and effectively eradicated with low-dose radiotherapy (18–20 Gy) [3,6]. Consequently, it is routine practice in several European countries to biopsy the contralateral testis at radical orchidectomy and treat TIN with radiotherapy. By adopting this policy a second orchidectomy can be avoided and only 25% will develop clinically relevant androgen insufficiency [3]. However this approach is controversial for several reasons.

First, the early studies showing low-dose radiotherapy (20 Gy) to be an effective treatment for TIN referred to the eradication of TIN at 2 years [6]. However, it has since been reported that both TIN and testicular cancer can recur within 5 years of completing radiotherapy for TIN, despite a negative biopsy at 18 months [7].

Second, only 5% of patients with testicular cancer have TIN so almost all the biopsies will be unnecessary [4]. Testicular biopsy can lead to problems with subsequent tumour diagnosis, pain, infection, infertility, testicular dysfunction and emotional distress, so this could generate significant excess morbidity [8]. Patients with risk factors (e.g. testicular atrophy, cryptorchidism and elevated LH or FSH) are more likely to have TIN [3]. However, in a series of 1188 patients undergoing contralateral biopsy at radical orchidectomy, 38% of those in whom TIN was found had no risk factors [4]. Therefore, restricting testicular biopsy to those patients with risk factors may not be a safe way to reduce the number of unnecessary biopsies.

Finally, secondary testicular tumours usually have a favourable prognosis [8], so the question of whether diagnosing and treating TIN improves survival is debatable. Nevertheless, we consider that high-risk patients should be offered a contralateral testicular biopsy at radical orchidectomy. However, they should decide for themselves whether to proceed, after a full discussion of the potential risks and benefits.

Patients with a solitary testis have achieved successful paternity despite the presence TIN, so patients may wish to defer radiotherapy to achieve natural conception [3]. However, they need to be aware that TIN severely impairs fertility and can progress to invasive cancer at any time [3].

Chemotherapy can also reduce the extent of TIN and the incidence of bilateral testicular cancer [3], but this is unreliable and the relative risk of subsequent tumour diagnosis has been reported to be 21% and 42% at 5 and 10 years, respectively [3].

THE ROLE OF SELF-EXAMINATION

Self-examination and early referral result in secondary testicular tumours being diagnosed at an early stage, as reported in a series of 30 bilateral testicular cancers, of which 25 were detected by self-examination, 83% were stage I and 17% were stage IIa [8]. Patients should therefore examine themselves regularly after radical orchidectomy and, as secondary testicular tumours have occurred after an interval of 25 years and follow-up often ceases after 10 disease-free years, this practice should be lifelong.

The NICE manual suggests that there is no evidence to support teaching self-examination in young men [1]. Whereas this may be applicable to the general population, patients with a history of cancer are likely to be more motivated. Indeed, the value of self-examination has been shown in this population and should therefore be encouraged [8]. However, it is known that patients are not always aware of the risk of relapse after radical orchidectomy, so education is essential [9].

TREATMENT OF BILATERAL TESTICULAR CANCER

CONVENTIONAL TREATMENT

Albers *et al.* [8] evaluated the pathology of 30 secondary testicular tumours and found most to be stage I. In addition, both proliferation rates and vascular invasion were less than that in the primary tumour [8]. Albers *et al.* also reviewed nine published series of bilateral tumours and found that, of 93 patients with follow-up data, only one died from recurrent disease. Coogan *et al.* [10] reported similar findings in a series of 21 bilateral tumours and found that, providing patients were properly staged, the outcome with conventional treatment was comparable to that for unilateral disease. Bilateral testicular cancer can therefore be treated in the same way as unilateral disease and patients should expect a similarly good outcome. However, radiation doses may have to be limited and retroperitoneal lymph node dissection might not be possible if it has been performed previously.

ORGAN-PRESERVING SURGERY

Testis-preserving surgery has been developed as an alternative to radical orchidectomy, with the advantage that physiological androgen production, body image and fertility can all be

TABLE 1 Types of androgen replacement therapy available in the UK

Preparation	Route (% of all used in UK)	Dosage	Problems	Benefits
Testosterone undecanoate*	Oral (24)	2–4 capsules of 40 mg/day (with meals)	Testosterone levels often subtherapeutic. Frequent dosing. Poor improvement in sexual function	Safe
Testosterone enantate cypionate proprionate	Intramuscular injection (43)	200–250 mg every 2–3 weeks 200 mg every 2 weeks 20–50 mg every 0.3–3 weeks	Androgen levels supranormal after dose and subtherapeutic at end of dose interval. Symptoms associated with fluctuation in androgen levels (mood swings, fluctuating libido and sexual activity, sweating and flushing). Injection pain	Patients maintain good quality of life and adequate sexual function after bilateral orchidectomy
Transdermal patch				
Testoderm Androderm Andropatch	scrotal (10) nonscrotal	1 × 5 or 2.5 mg /24 h	Scrotal shaving Noise from implants Must keep patch dry Skin reactions Transdermal system for nonscrotal skin more allogenic Adverse events in 7–84%	Bone and muscle structure maintained or improved. Improved sexual function Physiological circadian replacement of testosterone Readily reversible
Testosterone implant	subcutaneous (23) implant	3–6 100–200 mg implants every 6 months	Bleeding, dislodgement, infection in up to 11%. Not advisable if adverse effects likely as reversal is difficult	Infrequent dosing needed Sustained eugonadal replacement. Few adverse effects and well tolerated. Cost effective. Improved sexual function

preserved. The largest series to date comprised 73 patients with a mean tumour size of 15 mm [11]. The tumour bed was extensively biopsied in all cases. TIN was detected in 82% and treated with radiotherapy (18 Gy). After a median follow-up of 7 years, 72 patients (99%) had no evidence of disease and one had died from systemic recurrence. Four patients without TIN developed recurrent disease but were successfully treated with radical orchidectomy. Five of 10 patients who attempted paternity were successful, which compares favourably to the use of cryo-stored semen, where paternity was achieved in about a third of cases [12]. Only 9.6% developed de-novo hypogonadism.

Despite these encouraging results, organ-preserving surgery is still largely experimental. In our practice, all patients with whom we have discussed this have chosen conventional surgery, as the lifetime risk of recurrence cannot be quantified and the principal lasting gain is avoidance of hypogonadism.

Testosterone replacement is mandatory after bilateral orchidectomy to prevent the adverse effects of hypogonadism. However, the available preparations vary considerably (Table 1) and patients may need to sample more than one approach before they find one that suits them.

Oral testosterone: Serum testosterone levels have been shown to fluctuate widely after oral replacement in numerous studies, so this form of replacement is not recommended for complete hypogonadism, such as would occur after bilateral orchidectomy [13,14]. However, GPs frequently prescribe oral testosterone and it accounts for 24% of testosterone prescribed in the UK [13].

Intramuscular testosterone injections frequently result in serum testosterone levels that are initially supra-physiological and then decline to subtherapeutic concentrations towards the end of the 2–3 week dosing interval [14–16]. In two studies, evaluating a total of 50 patients after bilateral orchidectomy, testosterone levels were subtherapeutic at some point during the dosing interval in 55–86% of patients [15,16]. This was reflected in adverse effects (mood swings, reduced libido and hot flushes) towards the end of the dosing interval in 26–43% of patients [15,16]. These symptoms could be reduced by cutting the dosing interval from 2 to 3 weeks but most patients found injections tiresome [16].

Transdermal patches: Transcutaneous delivery devices release testosterone in a circadian pattern, which is more physiological than in the other approaches [14]. Several clinical trials have established that this approach achieves consistently eugonadal testosterone levels and the physiological effects of hypogonadism are avoided [14]. Patches are applied to scrotal skin (which has to be shaved) or other skin (where a permeation enhancer is required to improve absorption) [14].

Skin irritation, which is more common with permeation-enhanced devices, is the principal

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adverse effect and most clinical trials report that ≈10% of patients stop treatment for this reason [13,14]. However, a study evaluating the first nonscrotal patch released in the UK (Andropatch™, GSK, UK) found skin irritation to be an adverse effect serious enough to stop treatment in 52%, so it may be a more significant problem in clinical practice [13]. Topical steroids can reduce skin irritation and new delivery systems or testosterone gels may improve patient acceptability to the level seen with oestrogen replacement [13,17,18].

Testosterone implants: Subcutaneously implanted testosterone pellets release testosterone slowly as they break down, achieving physiological testosterone levels for up to 4–6 months [14]. A randomized controlled trial comparing pellets to intramuscular or oral testosterone showed that only pellets achieved consistently eugonadal serum testosterone levels [19]. Complications such as dislodgement and infection occur in ≈10% of cases but patient acceptance is high [14].

RISKS AND MONITORING OF TESTOSTERONE REPLACEMENT

Suboptimal testosterone replacement results in osteoporosis, so hypogonadal men receiving androgen replacement should undergo regular bone densitometry [14]. Also, although testosterone replacement increases the PSA level and prostate volume in hypogonadal men, these changes are within normal limits and there is no conclusive evidence that the risk of prostate cancer is increased [14,20]. However, older patients should be screened for prostate cancer, as it is a contraindication to replacement and may be unmasked by treatment [14]. Other potential adverse effects include polycythaemia and an increase in cardiac risk profile because of greater blood viscosity, changes in lipoproteins and insulin resistance [14].

Given these issues and the variability among testosterone formulations we recommend that an endocrinologist undertake the management of hypogonadism after orchidectomy, to ensure optimal replacement and monitoring.

TESTICULAR IMPLANTS

The NICE manual indicates that all patients being considered for radical orchidectomy should be offered testicular implants [1]. However, in one study, although 96% of patients felt this to be important, a third were not offered an implant and third declined one [21].

Two recent studies have addressed patient satisfaction after insertion of a testicular prosthesis [21,22]. Patients were assessed by a questionnaire, and complications and patient dissatisfaction were reported by 17% and 27% of subjects, respectively [21,22]. Frequent complaints were that the implant was too high or felt unnatural, and 5–10% wished they had not had one inserted [21,22]. Patients should therefore have a realistic expectation of the likely cosmetic result and an opportunity to see the implant before insertion. This practice, although common in breast reconstruction, has not been widely adopted by urologists [21]. However, 68% of men felt that their body image was improved and the implants did not impair sexual function [22].

The decision to have a testicular implant should be made at the primary operation, as previous surgery increases the complication rate and two-thirds of those who did not have an implant were unwilling to undergo a second operation [21].

The testicular implants used in the UK are silicone-based and, although leaks can occur, this is rare and does not seem to have any clinical implications [21–23]. As with other silicone implants, MRI is the investigation of choice for evaluating potential leaks [23]. Particle shedding can also occur but there is no conclusive evidence linking silicone prosthetics to auto-immunity, connective tissue disease or malignancy [22].

SEMEN STORAGE AND ASSISTED REPRODUCTION

The NICE manual recommends that all men undergoing radical orchidectomy be offered semen cryopreservation, as their treatment or disease may subsequently impair fertility [1]. However, the ethical issues surrounding semen storage are controversial, so both patients and their partners should have a clear understanding of the risks, benefits and legal aspects from the outset.

The largest reported series of patients who had semen stored comprised 930 men, and 37% had testicular cancer [12]; 9% of survivors attempted conception and a third were successful, with intracytoplasmic sperm injection being the most efficient reproductive technique [12]. Most semen was used within 5 years and only one successful pregnancy resulted from semen stored for >11 years, so the authors suggested that semen could be discarded after 10 years [12]. However, new techniques of storage may extend this period, and the duration of storage did not limit the time to pregnancy.

Testicular cancer, TIN and orchidectomy all impair semen quality and quantity significantly [12,24]. However, new reproductive techniques now mean successful pregnancy is possible using very poor quality semen [12] or even gametes taken directly from the testis in azoospermic individuals [25]. Semen storage and other techniques of assisted reproduction should therefore be available to all men undergoing orchidectomy for cancer who have not completed a family.

There is some suggestion that pregnancies arising from intracytoplasmic sperm injection are associated with a higher incidence of birth defects, but this has not been confirmed by other studies [12]. However, the outcome of such pregnancies arising from patients with cancer is less well known [12] so patients need to be aware of the potential risk and offspring should be monitored closely.

An important ethical and legal consideration is what happens if the donor dies before the semen is used. Under UK law, providing the donor has provided written, informed consent, posthumous use of semen is permitted [26] and a successful pregnancy has been achieved using semen stored by a donor before his death from testicular cancer [27]. However, this is ethically contentious and illegal in many countries. Even in the UK, 27% of fertility centres will not permit the posthumous use of semen [28]. The Human Fertilization and Embryology Authority requires semen to be moved to a centre willing to use it in this situation [28].

PSYCHOSEXUAL MORBIDITY AND QUALITY OF LIFE

Sexual dysfunction has been reported by 40% of patients being treated for testicular cancer and this does not appear to be significantly influenced by disease or treatment [29].

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Sexual dysfunction in testicular cancer is instead thought to be largely a consequence of the psychological impact of life-threatening illness, so one would expect men with bilateral tumours to be particularly at risk from this [30].

One study formally assessed psychosexual function and quality of life after bilateral orchidectomy [16]; 30 patients, all receiving intramuscular androgen, were assessed by validated questionnaires, and although 17 were hypogonadal despite androgen replacement, it was concluded that most were psychosexually well adjusted [16]. However, it was significant that 19% were affected by avoidance and, although their quality of life was better than in men with penile cancer, it was equivalent to that seen 1 year after radical mastectomy for breast cancer [16]. Five patients (10%) had significant post-traumatic stress [16]. An important role of the multidisciplinary team should therefore be to ensure that such patients are offered appropriate psychological support.

CONCLUSION

Most patients with bilateral testicular cancer will be cured, so a good quality of life is an especially important outcome, and this is also a key aim of the NICE manual. With careful management and support from a cancer centre multidisciplinary team most patients should achieve this. However, further work is required to establish if strategies such as organ-preserving surgery, treatment of TIN and new testosterone formulations can improve the quality of life further.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. **NICE.** *Improving outcomes in urological cancers – the Manual.* UK, National Institute for Clinical Excellence. September 2002
2. **Colls BM, Skelton HVJ, Thompsom PI, Framptom CM.** Bilateral germ cell testicular tumours in New Zealand. Experience in Auckland and Christchurch 1978–94. *J Clin Oncol* 1996; **14**: 2061–5
3. **Dieckmann KP, Skakkebaek NE.** Carcinoma in situ of the testis: review of biological and clinical features. *Int J Cancer* 1999; **83**: 815–22
4. **Loy V, Dieckmann KP.** Prevalence of contra-lateral testicular intra-epithelial neoplasia (carcinoma in situ) in patients with testicular germ cell tumour. *Eur Urol* 1993; **23**: 120–2
5. **Dieckmann KP, Souchon R, Hahn E, Loy V.** False negative biopsies for testicular intra-epithelial neoplasia. *J Urol* 1999; **162**: 364
6. **Giwercman A, Von der Maase H, Berthelsen JG, Rorth M, Bertelsen A, Skakkebaek NE.** Localised irradiation of the testis with carcinoma in situ: effects on Leydig cell function and eradication of malignant germ cells in 20 patients. *J Clin Endocrinol Metabolism* 1991; **73**: 596–603
7. **Dieckmann KP, Lauke H, Michl U, Winter E, Loy V.** Testicular germ cell cancer despite previous local radiotherapy to the testis. *Eur Urol* 2002; **41**: 643–50
8. **Albers P, Goll A, Bierhoff-Schoeneich G, Muller C.** Clinical course and histopathologic risk factor assessment in patients with bilateral testicular germ cell tumours. *Adult Urol* 1999; **54**: 714–7
9. **Young BJ, Bultz BD, Russell JA, Trew MA.** Compliance with follow-up of patients treated for non-seminomatous testicular cancer. *Br J Cancer* 1991; **64**: 606–8
10. **Coogan CL, Foster RS, Simmons GR.** Bilateral testicular tumours – management and outcome in 21 patients. *Cancer* 1998; **83**: 547–52
11. **Heidenriech A, Weibach L, Holtl W *et al.*** Organ sparing surgery for malignant germ cell tumour of the testis. *J Urol* 2001; **166**: 2161–5
12. **Kelleher S, Wishart SM, Liu PY *et al.*** Long-term outcomes of elective human sperm storage. *Human Reprod* 2001; **16**: 2632–9
13. **Parker S, Armitage M.** Experience with transdermal testosterone replacement for hypo-gonadal men. *Clin Endocrinol* 1999; **50**: 57–62
14. **Zitzmann M, Nieschlag E.** Hormone substitution in male hypo-gonadism. *Mol Cellular Endocrinol* 2000; **161**: 73–88
15. **Van Basten JP, Van Driel MF, Jonker-Pool G.** Sexual functioning in testosterone supplemented patients treated for bilateral testicular cancer. *Br J Urol* 1997; **79**: 461–7
16. **Fossa SD, Opjordsmoen S, Haug E.** Androgen replacement and quality of life in patients treated for bilateral testicular cancer. *Eur J Cancer* 1999; **35**: 1220–5
17. **Wang C, Swedloff RS, Iranmanesh A *et al.*** Trans-dermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypo-gonadal men, testosterone gel study group. *J Clin Endocrinol Metabolism* 2000; **8**: 2839–53
18. **Wilson DE, Kaidbey K, Boike SK, Jorasky DK.** Use of topical corticosteroid pre-treatment to reduce the incidence and severity of skin reactions associated with testosterone trans-dermal therapy. *Clin Ther* 1998; **20**: 299–306
19. **Conway AJ, Boylan LM, Howe C, Ross G, Handelsman DJ.** Randomized trial of testosterone replacement therapy in hypo-gonadal men. *Int J Androl* 1988; **11**: 247–64
20. **Slater S, Oliver RT.** Testosterone: its role in the development of prostate cancer and potential risk from use as hormone replacement therapy. *Drugs Aging* 2000; **17**: 431–9
21. **Ashead J, Khoubehl B, Wood J, Rustin G.** Testicular implants and patient satisfaction: a questionnaire-based study of men after orchidectomy for testicular cancer. *BJU Int* 2001; **88**: 559–62
22. **Inrocci L, Bosch JL, Slob AK.** Testicular prostheses, body image and sexual function. *BJU Int* 1999; **84**: 1043–5
23. **Hage JJ, Taets Van Amergongen AHM, Van Diest PJ.** Rupture of silicone gel filled testicular prosthesis: causes, diagnostic modalities and treatment of a rare event. *J Urol* 1999; **161**: 467
24. **Jacobsen K, Fossa S, Bjoro T, Aass N, Heilo A, Stenwig A.** Gonadal function and fertility in patients with bilateral testicular germ cell malignancy. *Eur Urol* 2002; **42**: 229
25. **Res U, Res P, Kastelic D *et al.*** Birth after treatment of a male with seminoma and azoospermia with cryo-preserved-thawed testicular tissue. *Human Reprod* 2000; **15**: 861–4
26. **Anonymous.** *The HEFA Act.* Chapter 37. London: The Stationary Office, 1990

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27 **Ahuja KK, Masimo J, Emmersom G *et al.*** Pregnancy following intra-cytoplasmic sperm injection treatment with dead husbands spermatozoa: ethical and policy considerations. *Human Reprod* 1997; **12**: 1360–3
28 **Corrigan E, Mumford ES, Hull MGR.** Posthumous storage and use of sperm and embryos: survey of opinion of treatment centres. *BMJ* 1999; **313**: 24
29 **Jonker-Pool G, Van Basten JP, Hoekstra HJ.** Sexual functioning after treatment for testicular cancer. comparison of different treatment modalities. *Cancer* 1997; **80**: 454–64
30 **Jonker-Pool G, Van de Wiel HB, Hoekstra HJ *et al.*** Sexual functioning after treatment for testicular cancer – review and meta-analysis of 36 empirical studies between 1975 and 2000. *Arch Sex Behav* 2001; **30**: 55–74

Correspondence: B.J.R. Barrass, Department of Urology, Bristol Royal Infirmary, Bristol, BS2 8HW, UK.
e-mail: barnabybarrass@hotmail.com

Abbreviations: **NICE**, National Institute for Clinical Excellence; **TIN**, testicular intra-epithelial neoplasia.