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UROLOGIC ONCOLOGY

Review Article

A comparison of time taken to return to baseline erectile function following focal and whole gland ablative therapies for localized prostate cancer: A systematic review

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Abstract

Objectives: To systematically review erectile function (EF) outcomes following primary whole gland (WG) and focal ablative therapies for localized prostate cancer to ascertain whether the treatment modality or intended treatment volume affects the time taken to recover baseline EF.

Method and materials: A systematic review was performed according to the preferred reporting items for systematic review and meta-analysis statement. Inclusion criteria were men with localized prostate cancer treated with primary, ablative therapy. Primary outcome was the return to baseline EF measured with objective, validated symptoms scores. Secondary outcome was use of phosphodiesterase inhibitors or erectile aids. Meta-analysis was not performed owing to heterogenous outcome measures.

Results: Of 222 articles identified in February 2017, 55 studies which reported EF after ablative therapy were identified but only 17 used validated outcome measures and met inclusion criteria. WG cryotherapy was used in 2 studies, WG high-intensity focused ultrasound (HIFU) in 5, focal cryotherapy in 2, focal HIFU in 3, focal phototherapy or laser therapy in 4, vascular-targeted photodynamic therapy in 3, and irreversible electroporation in 2. WG cryotherapy was associated with a significant decline in EF at 6 months with minimal improvement at 36 months. Baseline IIEF-15 of patients undergoing focal HIFU fell 30 points at 1 month but returned to baseline by 6 months. The remaining focal therapies demonstrated minimal or no effect on EF, but the men in these studies had small foci of disease. The review is limited by lack of randomized studies and heterogenous outcome measures.

Conclusions: Most studies assessing the outcomes of focal therapy on sexual function were not of high quality, used heterogenous outcomes, and had relatively short follow up, highlighting the need for more robustly designed studies using validated patient reported outcome measures for comparison. However, FT in general resulted in less effect on EF than WG ablation.

Keywords: Focal therapy; HIFU; Cryotherapy; Erectile dysfunction

1. Introduction

Quality of life outcomes including maintaining erectile function (EF) are major factors in the decision to proceed with intervention in men with localized prostate cancer

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(LPC) [1]. Radical prostatectomy (RP), radiotherapy, and active monitoring for LPC are associated with equivalent survival at 10 years [2]. Moreover, 17% of men in the ProtecT trial had erections sufficient for intercourse following RP compared with 30% of those on active monitoring [3]. EF was reported with Expanded Prostate Cancer Index Composite (EPIC) scores unlike in most other LPC radical therapy trials where validated questionnaires have not been used routinely. Ablative therapy (whole gland [WG] or focal) was introduced with the hope of avoiding some of the adverse effects of radical therapy including erectile dysfunction (ED), bladder or bowel dysfunction, and urinary incontinence as well as avoiding the psychological burden of active monitoring. Ablative therapies for prostate cancer are now available in many European countries as well as Canada and the USA where high-intensity focused ultrasound (HIFU) was first approved by the Food and Drugs Administration in 2015 [4].

Prostate cancer was initially believed to be a multifocal disease [1]. However, histological studies have demonstrated single foci or significant disease in just one half of the prostate [1]. More recently, whole genome sequencing of areas of prostate cancer and normal prostate tissue within single prostate glands have shown common mutations within the cancer and in the normal tissue suggesting there is a "field effect" occurring within the WG [5]. It should be clear that a field-effect is not necessarily indicative that new aggressive tumors will develop in untreated tissue as evidenced by the safe management of patients with active surveillance [2].

Alongside improving imaging and biopsy techniques including magnetic resonance imaging (MRI) fusion, novel understanding of the pathology initiated focal therapy (FT). Ablative energy sources include cryotherapy, HIFU, laser or photodynamic therapy (PT), and irreversible electroporation (IRE). Cryotherapy was one of the first ablative techniques to be introduced [6]. It induces cell lysis by cooling tissues to –40°C [7]. Autonomic dysfunction occurs if the nearby neurovascular tissues are cooled to 3°C, which may be irreversible at −20°C, which accounts for the high rates of ED observed after WG cryotherapy. HIFU focuses ultrasound energy leading to tissue ablation via thermal coagulation necrosis and acoustic cavitation [8]. It has the potential of more precise ablation than cryotherapy but many men nevertheless report ED. PT induces cell death via cytotoxic oxidative stress. IRE uses pulses of direct current to create nanopores within the cell membrane leading to apoptosis [9–11].

There are no published randomized controlled trials comparing oncological outcomes of radical therapy and FT for LPC. The PART study is currently in the pilot phase, randomizing men with intermediate risk disease to RP and FT [12]. If ablative therapies are to be offered as viable alternatives to radical treatment and active monitoring, men must be informed of the precise risks of ED in an objective and understandable manner. Currently, ED reporting after FT is not interpretable by patients as many studies within the existing literature either use their own definitions of ED or use no definition at all [13]. The change in pretreatment EF, time taken to return to this baseline level, and use of any support such as tablets, injections, or erectile aids, for example, Vacuum Erectaid would be meaningful to patients but are not routinely reported.

The effects on EF after ablative therapy have not been systematically reported and compared. This is particularly important for patient counseling as the incidence of decision regret in LPC is related to morbidity, particularly sexual morbidity and decision regret may be reduced by increased information and support before the decision [14,15]. This study aims to determine and compare whether the modality or intended treatment volume of ablative therapy, that is, focal or WG might affect the severity of ED and return to baseline function.

2. Material and methods

2.1. Search strategy

A systematic review of the Cochrane library, Scopus, and Pubmed was performed from inception to February 2017 according to the Preferred reporting items for systematic reviews and meta-analyses ("PRISMA") statement [16]. Search terms included "erectile dysfunction," "focal therapy," "ablation," "HIFU," and "cryotherapy." The full search for PubMed is shown in Appendix A. No time limit for publications was applied. The review was registered with PROSPERO (registration number 42016042070).

2.2. Study eligibility

Study eligibility was defined using the population, intervention, comparator, outcome, and study design approach. For inclusion, studies needed to include men with LPC treated with primary ablative therapy either as FT (intervention) or WG therapy (comparator) [17]. Studies needed to report validated EF outcomes such as the EPIC, the UCLA Prostate Cancer Index (UCLA-PCI), the prostate cancer quality of life survey, the 15 item International Index of Erectile Function (IIEF-15), or the shortened 5 item International Index of Erectile Function (IIEF-5) also known as the Sexual Health Inventory for Men (SHIM) score [18–20].

Included studies needed to contain 5 or more patients and report EF before ablative therapy with at least 6 months follow up. Studies reporting scores as ranges, duplicates, non-English language (if no translation available), reviews, case reports, letters, and nonfull text articles were excluded. N.F.W., J.N., and T.Y. independently reviewed eligibility and assessed bias at study level using Cochrane bias assessment tools. Incongruities were resolved by consensus of all authors.