FOCAL THERAPY FOR PROSTATE CANCER: A POTENTIAL STRATEGY TO ADDRESS THE PROBLEM OF OVERTREATMENT

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Summary.— Focal therapy for localized prostate cancer involves destroying the cancer focus in order to offer patients the potential of combining cancer control with minimal side-effects. Current standard of care involves either active surveillance or radical therapy. Neither of these is ideal. Active surveillance carries a risk of under-treatment, with psychological morbidity as a result of anxiety and is associated with side-effects due to repeated biopsies, although radical therapy is the gold standard for curative treatment. With the proportion of unifocal or unilateral disease among men with low-risk disease rising, a focal approach could avoid both under and overtreatment. With the advent of improved accuracy for cancer localization provided by multi-parametric MRI and new biopsy strategies such as transperineal mapping biopsies, ablative modalities such as cryotherapy, high intensity focused ultrasound, photodynamic therapy and radio-interstitial tumour ablation make focal treatments a real possibility.

Keywords: Focal therapy. Cryotherapy. HIFU. Photodynamic therapy. Prostate cancer.

Resumen.— La terapia focal entraña la destrucción del foco cancerígeno y el tejido circundante para ofrecer a los pacientes el potencial de combinar control oncológico y mínimos efectos colaterales. El tratamiento estándar actual incluye vigilancia activa o tratamiento radical. Ninguna de estas opciones es ideal. La vigilancia activa conlleva el riesgo de infratratamiento, morbilidad psicológica como resultado de la ansiedad, y no está libre de efectos colaterales debido a las biopsias repetidas. Aunque el tratamiento radical es el patrón oro del tratamiento curativo, conlleva riesgos de sobretratamiento con sus numerosos efectos colaterales. Con el aumento de la proporción de cánceres unifocales o unilaterales entre varones de bajo riesgo, un abordaje focal podría evitar tanto el infra como el sobretratamiento. Con la mejora de la precisión de la localización del cáncer proporcionada por la resonancia magnética nuclear multiparamétrica y las nuevas estrategias de biopsia como las mapas biopsicos transperineales, las terapias ablativas como crioterapia, ultrasonidos focalizados de alta intensidad (HIFU), terapia fotodinámica y ablación radiointersticial de tumores hacen del tratamiento focal una posibilidad real.
INTRODUCTION

Focal therapy for localized prostate cancer is a new therapeutic strategy that was recently added to the armamentarium of management approaches that could be adopted as an alternative to active surveillance and the numerous radical therapies already in practice. This article will outline why the standard options for men are not ideal. Secondly, we discuss improvements in cancer localization with MRI and biopsies and the current literature base on the focal therapy treatments available (1,2). Finally, we will discuss which patient group is best placed to receive focal therapy.

Concept of focal therapy

Management of localized prostate cancer currently consists of two extremes: active surveillance on the one hand and radical treatment on the other. A greater proportion of localized low to intermediate risk prostate cancers are now detected due to PSA screening. Men with localized prostate cancer are often young and have a life expectancy of more than 15 years. The vast majority of men are not keen on the functional and quality of life outcomes that are traditionally associated with radical therapy but also want to have their cancer controlled. There is a lack of long-term data from active surveillance protocols coupled with the inability at the moment to reassure men that they have been accurately risk stratified and do not have a higher risk disease which could result in adverse outcomes. A focal treatment, destroying the cancer focus and a small margin of normal tissue surrounding the cancer, may be a solution for these patients.

In recent years, different techniques of focal treatment have been evaluated and developed. This has largely been possible through improvements in prostate cancer localization, using imaging as well as prostate mapping biopsy techniques, as well as development of ablative techniques.

Problems of standard care

Active surveillance

Patients who fulfill current active surveillance criteria represent a very low-risk group. Criteria commonly used are PSA<10ng/ml, PSA doubling time>3 years, Stage T1c to T2a, Gleason<7, percentage of positive number of cores and tumor presence <50% of a single biopsy core (3-8). However, these criteria may not be strict enough as the diagnostic test that they are based on has significant random and systematic errors. It is not surprising therefore, that 1 in 4 to 1 in 3 men initially suitable for active surveillance were found to have higher Gleason grade or burden of cancer on repeated biopsies (9).

In addition, although active surveillance is thought to have no side-effects, as there is no treatment until progression, this assertion should be somewhat moderated. Active surveillance can involve deterioration of quality of life as shown by health questionnaires (10-13). We should also take into consideration the psychological burden of living with an untreated cancer with the uncertainty of disease progression and anxiety as well as healthcare and financial burdens associated with an intense surveillance programme. Some groups have tried to show the psychological consequences of active surveillance (14-16), finding higher anxiety levels due to surveillance. However, others did not find this (17).

Can we determine whether patients under this regimen will develop a non-curable cancer during the period of surveillance? Cases have been reported of patients who were thought to be suitable for active surveillance, but at radical prostatectomy were found to have more aggressive and in some instances incurable disease (i.e., extracapsular extension or lymph node metastases) (13,18). Many have argued that because we have a limited ability to predict which cancers can be safely observed without disease progression (19), surveillance should not be carried out in any men with prostate cancer (20).

Radical therapy

Once a localized prostate cancer is diagnosed, radical therapy remains the gold standard treatment with a curative intent. However, radical whole-gland therapies can give rise to significant side-effects with adjoining structures suffering damage and injury, such as bladder (especially bladder neck), neurovascular bundles, external rhabdosphincter and rectum. These can lead to reduced bladder capacity, urge incontinence, or bladder neck strictures, urethral strictures, stress incontinence, impotence and bowel toxicity (diarrhoea, bleeding, pain). The frequency of these effects dependent on the modality employed. Living with the side-effects of treatment could be worse than living with the disease itself, which may never progress or progress at such a slow rate that many men die.
of other causes (9). Despite surgery and radiotherapy showing improvements in their delivery, for example with laparoscopy and robotic surgery, or intensity modulated radiotherapy, the benefits of these over traditional surgical and radiotherapeutic approaches are limited with no significant improvements in quality of life after radical treatment (21,22).

**Focal therapy techniques**

**High intensity focused ultrasound (HIFU)**

High energy density is generated by the tight focusing of ultrasound waves. Therapeutic HIFU is usually delivered using low frequencies (3.5-4.5 MHz), causing heat and "inertial cavitation" and then tissue destruction. When temperatures rise to 56°C and this temperature is held for at least 1 second, tissue damage can occur, with resultant coagulative necrosis and an inflammatory response. In HIFU, the temperature achieved is typically above 80°C. Two transrectal devices currently exist: the Ablatherm® device (Edap-Technomed, Lyon, France) and the Sonata® 500 (Focus Surgery, Indianapolis, IN).

Recent review data regarding HIFU in the use of whole-gland ablation demonstrate five year-negative biopsy rates from 87% to 97% (1) (23, 24) with five-year disease free survival rates, according to ASTRO criteria, varying from 66% to 78% (1) (24). Reported side-effects using the whole-gland approach are incontinence (0.5%-15.4%), urethral stricture (24%), fistula (0-2%) and impotence (13-53%) (25). However, these side-effects are poorly reported (1). HIFU is promising because it allows precision in targeting lesions and it seems to have a low morbidity. In addition, MRI thermography could be coupled to the energy in order to permit temperature monitoring during the treatment.

**Cryotherapy**

Cryotherapy involves freezing and waving to destroy cancer. Tissue destruction is caused by vascular injury, direct cytolysis, ice crystal formation, intracellular dehydration, pH changes, cryoactivation of immune responses and induction of apoptosis. It also causes endothelial damage leading to platelet aggregation and micro-thrombosis. 3 minutes of freezing at a temperature of -0°C can ablate tissue effectively. 3rd generation devices for cryotherapy perform prostate cancer ablation with trans-rectal ultrasound guidance and urethral warmers. Small probes use pressurized gas that freeze, and then thaw the tissue. The probe size allows the surgeon to make a relatively precise treatment, so the damage to surrounding structures can be minimized. However, the lack of real-time feedback is problematic as all the user visualises is a hypoechoic ice-ball front which does not represent the temperature gradient accurately.

Cryotherapy is the most studied ablative therapy technique. Ahmed et al identified 13 cryotherapy series reporting extractable data, and found that, according to ASTRO criteria, cryosurgery has good biochemical control (25) using a whole-gland treatment. Using Phoenix criteria, it was found that there was 80.5% 10 year biochemical disease free survival for low-risk groups. The 5-year rate was 91.1%. 10-year rates for negative biopsy status was 73.8% (26).

Data from focal cryotherapy studies, although more recent and therefore limited by short follow-up, found biochemical disease free rates varying between 80% to 96% (9, 27 - 31) with disease-free survival of 84% at 3 years (26). However, comparison between studies is difficult since there is no agreed or validated measure of success or failure after focal therapy.

Morbidity seems to be diminished by focal cryotherapy, with a higher health related quality of life, due to lower rates of incontinence, fistula, or erectile dysfunction (32). A multicenter study of 106 patients, using 3rd generation devices, report morbidity rates in whole-gland cryotherapy of 5% urethral sloughing, 3% incontinence with pad usage, 5% urge incontinence without pads, 3.3% of transient urinary retention, and 2.6% rectal pain. Contemporary results for potency after focal cryotherapy are about 80-90% (26). Nevertheless, long-term data are still needed. We will soon be able to improve the evaluation of focal cryotherapy, as a result of large multicenter databases such as the COLD (Cryo On-Line Data) registry.

**Photodynamic therapy (PDT)**

This uses a photosensitizing drug that accumulates preferentially in tissue. The drug is then activated by light of a specific wavelength in the tissue or in the vasculature. Tissue oxygen is also required for the treatment effect. The activated drugs, create tissue damage. This technique is based on a transperineal approach, using a brachytherapy template to insert optical fibers that deliver low power laser light to activate an intravenously administered photosensitizer.

A few studies have been reported. Ahmed et al. found seven studies recently (25). Efficacy related
to this technique seems to be promising, but these are only preliminary results on PSA levels after treatment. In most of the published studies, there are no biopsy results. Trials are currently under way to evaluate this technique further. Preliminary results are encouraging, but improvements are to be made (33), and cancer control has yet to be confirmed (1).

Radiofrequency interstitial tumour ablation (RITA)

This new technology is performed by the transperineal approach, using percutaneous needles inserted under ultrasound guidance. Low-level radiofrequency energy heats and ablates tissue by coagulative necrosis. There are no studies on RITA for prostate cancer treatment and only a few historical reports on the use of this ablative technique in benign prostatic hyperplasia.

The need for accurate localization of the lesion

For many years, imaging of the prostate was by B-mode transrectal ultrasound imaging (TRUS). However, TRUS has a low sensitivity and specificity for prostate cancer with other prostatic pathologies like benign prostatic hyperplasia or prostatitis being hypoechoic as well. TRUS biopsies can only predict unilateral cancer in 27.6% of cases and this was not improved by adding other biopsy characteristics such as percentage tumour involved or number of positive biopsies (34). The number of necessary cores to correctly localize cancer is uncertain. A number of groups have stated that TRUS biopsies are not sufficient for tumour localization, or accurate staging or grading, in the case of selecting patients for a focal treatment (35-38).

Transperineal ultrasound guided (TPUS) biopsies can now be performed. Using a brachytherapy template, taking one core every 5mm, the extent and location of cancer can be mapped within the prostate. Different studies have shown that TPUS biopsies accurately demonstrate clinically significant prostate cancer with a high degree of sensitivity (37). Cancer detection rates increase from 29% - 34% for traditional techniques to 47-70% for TPUS biopsies (39,40), particularly in the anterior part of the gland that is inherently under-sampled by TRUS guided transrectal biopsies (35,37). TPUS also allows accurate Gleason grade to be determined (9, 37, 40). On simulation models, TPUS biopsies performed every 5mm could detect 95% of significant cancers defined by volume of 0.5cm³ (39). The toxicity and healthcare burden are the main disadvantages of TPUS biopsies. Although TPUS biopsies have a lower infection rate than TRUS biopsies the retention rate is higher with groups finding 5-10% rates of acute urinary retention even when alpha-blockers are used peri-procedure (35). Many groups have concluded that mapping biopsies should be recommended for selection of focal therapy patients (9,41,35,36). Some also point out that dissection difficulties can occur if a radical prostatectomy is then performed (19,37,35).

Adding colour Doppler seems not to improve the detection rate for small tumours although its role in significant tumours may be useful (42). Recently, contrast-enhanced TRUS (CE-TRUS) has shown some promise higher sensitivity for detection of cancer foci. The detection rate of clinically significant prostate cancers was improved in a number of studies (43-46) with the ability to provide real-time targeted biopsies (42). Prostate Histoscanning has also shown promise with a higher sensitivity and specificity for significant lesions as defined by a volume of 0.5cc but studies have been small and non-blinded. The results of a multicentre European blinded study currently under way are awaited (47, 48).

Multi-parametric MRI protocols are now showing encouraging results in detecting significant lesions, with a volume cut-off of 0.5cm³ or 0.2cm³, and in accurate localization of the cancer as well as cancer characterization (grade, extraprostatic extension) (49,43,50).

Image-guided treatment is also under development, with CE ultrasound (51,52) or MRI (53-56). Nevertheless, MRI-guided treatment is not currently ideal because of the magnetic environment, the problem of access to MRI, cost and patient discomfort (43). Combining imaging and histopathological data from prostate mapping biopsies appears possible to create the most accurate localisation of lesions to deliver focal therapy at the present moment.

Patients suitable for Focal Therapy

For the moment, there is no consensus about which criteria should be used to select men for focal therapy. With current trends of PSA screening and the lowered PSA threshold for biopsy, 45% to 85% of patients fall in the category of low-risk (PSA< 10 μg/L, Gleason grade 3 + 3, cT1c-cT2a). It is estimated that between 25% and 84% of men currently being treated would not succumb to their disease should their disease be left untreated representing significant over-diagnosis (13).

Prostate cancer is usually regarded as a multifocal disease. However, several studies, based on
radical prostatectomy specimens, found a significant proportion of men having either unifocal or unilateral disease. It has been reported that prostate cancer is unilateral in 16% to 63% (9, 21, 38, 57-60) and unifocal in 13% to 26% (9, 35, 61). This argument leads to the proposition that a substantial number of men could have a hemiablation approach to their disease. Interestingly, a recent study has found that unifocal cancers have a more aggressive behaviour than multifocal disease. In a series of 1159 radical prostatectomies, pathological examination found 18.7% versus 10.1% of Gleason 8 to 10 for unifocal and multifocal cancers, respectively. Furthermore, biochemical recurrence rates were 38.5% for unifocal disease versus 24.2% for multifocal disease.

Multifocal disease need not necessarily be excluded from focal therapy. Evidence points to men with multifocal prostate cancer being eligible for a form of focal therapy if ablation is targeted towards the index or significant lesions alone. A cut-off at 0.5 cm$^3$ (less than a diameter of 10mm) can be used to predict lifetime risk of mortality (62). 80% of secondary non-index lesions are less than 0.5 cm$^3$ (21, 35, 63, 64). Moreover, secondary cancer foci were found to have on average a cumulative volume less of 0.3 cm$^3$. 90% of extracapsular extension comes from the index lesion, and this index lesion represents 80% of the total tumor volume (13, 27, 35, 52-56, 65, 66). Presence and volume of the secondary cancer foci has no influence on biochemical recurrence after a radical prostatectomy (35). An important and interesting research question therefore involves focal therapy to treat the index lesion alone and surveillance of the secondary non-significant lesions (provided they are small and have Gleason 6 or less) (67). Indeed, one such trial is underway at the authors' centre (National Cancer Institute registration protocol number: NCT00988130).

A number of consensus groups have met to discuss recommendations for focal therapy. In 2006, first criteria appeared in the Consensus Conference on Focal Treatment: expectancy life $>5$ years, stage T1 to T3, PSA $<15$ng/ml, no M1 disease. They considered lymph node disease as a relative contraindication. They believe that PSA density, PSA doubling time, Gleason score and ploidy status should not be taken into account (36). Eggener et al, in the TASK Force group, proposed criteria to determine which patients should have focal therapy. They proposed criteria reflected those used in active surveillance. The very population, which argue, should not have any treatment. In other words, clinical stage T1–T2a, PSA less than 10 ng/ml, PSA density less than 0.15 ng/ml, PSA velocity less than 2ng/ml yearly, no Gleason 4 or 5, no evidence of extra-prostatic extension and a single lesion (68). Sartor et al add that a lesion with largest dimension of $<15$ mm in any plane by imaging with the lesion not exceeding 5mm of capsular contact on axial images should be used to define lesions on MRI. Furthermore, the regional nodes should not be suspicious for metastatic disease. In other words, they should measure $<7$mm in the short axis and have a smooth border, and there should not be an asymmetric cluster of nodes (35).

**CONCLUSIONS**

Focal therapy for prostate cancer represents a paradigm shift that may provide the middle way between under-treatment and over-treatment offering ablation of the cancer and preservation of non-malignant tissue and surrounding vital structure in order to lower side-effects.

Recent advances in cancer localization using imaging (multi-parametric MRI, tissue ultrasound characterisation, contrast-enhanced ultrasound) have shown encouraging accuracy rates in detection as well as localization of prostate cancer. TPUS biopsies, which map the prostate every 5mm, arguably provide the ideal accuracy in cancer localization and characterisation for delivering focal therapy but carry a healthcare burden. Trials are needed to assess feasibility, efficacy and safety of focal therapy. Many of these trials are currently in process and if the early signs of lower toxicity are verified then planning for larger long term studies is needed either using cohort designs or comparative pragmatic designs to assess focal therapy against active surveillance and radical therapies.

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