Focal Therapy in Prostate Cancer: A Review of Seven Common Controversies

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Abstract

Radical treatments such as prostatectomy and radiotherapy have demonstrated success in terms of biochemical and disease-specific survival for localised prostate cancer. However, whilst the end goal of any cancer treatment is to control or cure disease it must also do so by minimising any side effects that may be experienced by the patient. Focal therapy as a concept aims to redress this established therapeutic ratio by treating areas of the prostate affected by significant disease as opposed to treating the entire gland. However, there are a number of common criticisms of focal therapy - we deem the seven sins - that require further interrogation.

Key words

Prostate cancer; Focal therapy; Arguments for; Arguments against

Introduction

Radical treatments such as prostatectomy and radiotherapy have demonstrated success in terms of biochemical and disease-specific survival for localised prostate cancer[1-3]. However, whilst the end goal of any cancer treatment is to control or cure disease it must also do so by minimising any side effects that may be experienced by the patient. Focal therapy as a concept aims to redress this established therapeutic ratio by treating areas of the prostate affected by significant disease as opposed to treating the entire gland. However, there are a number of common criticisms of focal therapy – we deem the seven sins – that require further interrogation and summarised in table 1.

Reason 1 - 'Prostate cancer is multifocal'

This is true. Studies of whole-mount prostate specimens have demonstrated that in the majority of cases, multifocal disease is present[4]. However, in 15% of men the disease is truly unifocal[4]. Despite this, multifocality in itself need not preclude focal therapy considering the biology of the disease and its status as an outlier in solid organ cancer therapy. Prostate cancer is largely isolated where radical therapy remains the gold standard treatment. By comparison, despite initial and stalwartly

held beliefs, the last two decades have seen the widespread acceptance of subtotal thyroidectomy, partial nephrectomy, partial penectomy, subtotal pancreatectomy and lumpectomy in breast cancer in preference to their more radical counterparts.

Breast surgeons have, in recent years, made great efforts to focus the treatment of breast cancer on the tumour rather than the whole breast. This is clearly reflected in wide local excision replacing the radical mastectomy as the primary treatment for ductal breast carcinoma. This was reported as early as 1992[5] despite up to 75% of these malignancies being multifocal[6]. Naturally, concerned voices dissented[7]. Many argue that breast cancer is no similar to prostate cancer as adjuvant radiotherapy still targets the whole breast after wide local excision. However, more recent studies have demonstrated that the tumour focused approach to treatment has equivalence in outcome when compared to a more radical approach. For example, a randomized controlled trial built on established knowledge that even in the presence of multifocality, 90% of local recurrences occur in the index quadrant. The trial compared targeted intraoperative radiotherapy to external beam radiotherapy following breast-conserving surgery[8]. No difference was found in tumour recurrence between the groups[8]. Indeed, overall survival was slightly better in the targeted radiotherapy arm due to a reduction in radiation-induced toxicity to the heart and lungs[8].

Similarly, the treatment of renal cell carcinoma has seen a clear shift from radical nephrectomy to nephron sparing surgery. Much like with breast cancer there was initial controversy. Authors called for the re-evaluation of the indications for partial nephrectomy due to the presence of satellite lesions or nodules found in whole organ pathology specimens[9], which would be left behind following nephron-sparing surgery. Once again, evidence of overall survival equivalence began to build until a randomised controlled trial (RCT) of 541 patients demonstrated no significant difference in overall survival between patients undergoing partial or radical nephrectomy for renal cell carcinoma[10]. It is of interest, that practise and guidelines had changed many years prior to this RCT based on prospective cohort studies.

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Thus, in both these examples the suggestion is that lesions which are inevitably left behind by a more focal or less aggressive treatment do not go on to metastasise, or at least not within a significant period of time. In prostate cancer there is now clear evidence that (on the whole) it is the largest, highest grade index lesion that drives the progression to local invasion and metastases. First, one can look at the histological prognostic characteristics observed in whole-mount prostate specimens. When extracapsular extension or seminal vesicle invasion is present, it is predominately within the index lesion. Karavitakis et al demonstrated that where these features are seen in satellite lesions, they are also high grade and high volume[11]. In their analysis of 100 radical prostatectomy specimens they showed that whilst the majority of specimens had multifocal (78%), or bilateral (86%) disease, 99.4% of these satellite lesions were of Gleason 6 grade or less and 87% were less than 0.5ml in volume[11]. Furthermore, when Bott et al investigated the tumour volume and its relationship with tumour grade, most high-grade disease, i.e. Gleason 7 or higher, resided in larger volume tumours[12]. However, Gleason 7 or higher disease was also found in 10% of <0.5ml tumours and 5% of <0.2ml tumours[12]. In these cases however, the grade was predominantly Gleason 3+4[12].

When one delves deeper, from the microscopic to the molecular level, there is clear evidence that it is the index lesion that drives the metastatic process. In other words, the genomic profiles of prostate cancers and their metastases imply that the latter originate from a single clone[13]. Liu et al demonstrated from their genomic analysis of 85 tumour sites in 29 men, that the metastases were likely to have a common clonal origin[14]. However, they could not link them to individual lesions within the prostate itself[14]. Likewise, the importance of *TMPRSS2-ERG* fusion in prostate cancer has been documented for some time[15]. More relevant to this arena however, is the concordant presence of this abnormality in both the index lesion and lymph node metastases[16] and multiple metastases exhibiting *TMPRSS2* aberrations of indistinct molecular subtypes[17]. We can conclude from these observations that metastatic deposits in prostate cancer originate from a single precursor cancer cell[14,16,17] and that these are most likely to arise from the index lesion in multifocal disease[16].

Regardless, one could ask what the clinical implications are for these observations. The inference is that low grade; low volume disease does not need to be treated. In addition to these histological and molecular studies there is now substantial, and perhaps more tangible, clinical evidence to support this. In particular, there is now strong evidence that low grade disease is unlikely to lead to metastasis and death. For example, Ross et al in a study of 14000 aimed to determine whether or not in men with pure Gleason 6 cancer, their disease had the potential to metastasise[18]. In each of the 22 cases of lymph node metastasis, a review of their whole mount specimens found that they all had higher-grade disease[18]. The authors remarked "it can now be concluded that GSr6 using the updated system lacks the potential to metastasise to pelvic lymph nodes"[18]. Klass et al reported on a prospective cohort of 1300 men with low risk prostate cancer[19]. Of this group, only 93 (7%) had died from their disease at 15 years of follow-up[19]. This suggests that whilst low-risk, these cases still convey some mortality. However, further evidence suggests that such mortality is due to errors in risk stratification at diagnosis. Eggener et al in a study investigating the long-term outcomes in a retrospective cohort of 9557 men who underwent surgery for pure Gleason 6 disease, regardless of tumour volume[20]. In this group only three died over a 15-year period[20]. However, when the pathological specimens were re-examined in these men, they all had higher-grade disease, which had initially been overlooked[20]. Thus, of 9554 men, none died from their prostate cancer within 15 years[20]. This suggests that whilst low-risk, these cases still convey some mortality. However, further evidence suggests that such mortality is due to errors in risk stratification at diagnosis. Such is this weight of evidence for low volume Gleason 6 disease behaving in an indolent manner that a number of groups have advocated its re-designation as a benign entity[21].

However, conflicting evidence might exist, in rare instances. For example, a single case report by Haffner et al described whole-genome sequencing of metastatic deposits in a man who died from lethal, metastatic prostate cancer 17 years after diagnosis[22]. This defined the genetic characteristics of the lethal disease. This was then compared to the whole mount prostatectomy specimen removed at surgery 17

years previously. Unsurprisingly, there was substantial heterogeneity within the primary tumour[22]. It appeared that the lethal clone had arisen from a small focus of Gleason 6 disease surrounded by a larger area of high-grade disease[22]. The lymph node metastases also appeared to be from a different clonal origin[22]. Concern was rightly raised and asked questions regarding not only the index lesion hypothesis but also called into question the current dogma that these tumours do not develop lethal, metastatic potential. This man had died from disease that would be considered today as low-risk for progression[23]. This was touched upon by Barbieri et al who argued, after examining the prostatectomy specimen, that several areas of the gland contained the same *SPOP*-mutation, alongside significant proportions of Gleason 4 disease, and these are likely to be the same tumour[24]. They concluded that in this case, the lethal tumour began "as a relatively large, *SPOP*-mutant tumor displaying significant amounts of Gleason pattern 4"[24]. Most importantly, the presence of a small focus of Gleason 6 tumour within a larger volume high-grade tumour would not have had implications on clinical decision making[24] and certainly was not the same as a single tiny focus of Gleason 6 disease on its own. Were that to be the case, and taking the arguments proposed by some authors that we should be cautious if leaving Gleason 6 disease untreated[25], one-third of the male population would need to have a prostatectomy – a clearly ridiculous notion. A similar picture emerged from a case report from the Johns Hopkins University once again. Haffner et al described a man who chose to enter active surveillance for low grade, low volume prostate cancer, who subsequently developed high grade, high volume disease, which he consequently died from[26]. Immunohistochemical staining revealed positivity for *ERG* and *TP53,* which was not shared by the earlier biopsy core taken during active surveillance[26]. Furthermore, the *Ki-67* proliferation index was low for the cores during active surveillance but dramatically higher in the later, high-grade biopsy[26]. They concluded that rather than this case demonstrating lethal progression from the initially diagnosed tumour, the lethal disease arose from a clonally distinct anterior tumour, which was not sampled on TRUS biopsy[26]. This supports our position that not all lesions are clinically important in terms of progression and lethality. In yet another example, Grasso et al showed in a case report of a man with coeliac lymph nodes metastases,

lung metastases and bladder metastases that a Gleason 9 tumour identified on a whole-mount prostatectomy specimen was the monoclonal origin of the disease process[27]. Once again, this supports our position, namely that progressive disease derives from a single point of origin. These are n=1 case reports and as such lack significant weight, despite being intriguing anecdotes. However, studies investigating the genomic basis of prostate cancer and the natural evolution of the disease process will inevitably add far greater insight.

With what we now know, can we truly state that the multifocal nature of prostate cancer renders focal therapy ineffectual? If it is rare, but not impossible, for men with pure Gleason 6 disease to metastasise, is it too great a leap to propose that secondary lesions in a man with a clinically significant index lesion will also rarely metastasise?

Reason 2 – 'You cannot accurately localise prostate cancer lesions.'

Whilst this might be true of the TRUS biopsy which we know gets the grade or side of cancer wrong in between 30-50% of cases with low risk or unilateral cases, respectively[28], as things stand currently, we have excellent diagnostic tools that are not only highly sensitive at detecting cancer within the prostate, but also accurately determine the locality of disease within the gland. Firstly, there is transperineal template mapping biopsy. Appropriate criticisms have been made of the technique, of course. These include the risk of over diagnosis, additional burdens on patients and healthcare systems and a steeper learning curve for clinicians to climb as well as costs and resource issues. However, the ability of the technique to accurately localise disease within the prostate might outweigh these disadvantageous caveats.

For example, computer simulation has demonstrated that mapping biopsy is far more accurate than the transrectal biopsy[28]. These simulations, performed on 107 whole mount prostatectomy reconstruction models demonstrated that transperineal mapping biopsy missed only 5% of tumours >/=0.2mL and >/=0.5mL compared to 30-40% in traditional transrectal biopsy[28]. Optimised transrectal biopsy strategies

were better than standard transrectal biopsy, but still inferior to transperineal mapping strategies[28]. Clearly, we still, as a professional community base our pathway on a demonstrably poor test. Furthermore, Crawford et al, in direct comparison of 25 men who underwent transperineal mapping biopsies with their reconstructed whole mount prostatectomy specimens following surgery showed that this biopsy strategy was highly accurate[29]. Indeed, of 64 tumours only a single significant Gleason 8 0.02mL tumour was missed at biopsy[29]. However, as we have previously mentioned transperineal mapping biopsies do carry disadvantages and additionally, once identified and localised, how can we stratify the risk of potential lethality for each patient? We would advocate a system that takes into account the Gleason grade, and the lesion volume derived from the surrogate measurement of maximum cancer core length. One such example is our own UCL criteria, i.e. definition one being the presence of Gleason >/=4+3 and/or maximum cancer core length >/=6mm and definition two was the presence of Gleason >/=3+4 and/or maximum cancer core length >/=4mm[28]. Gleason </=6 and/or </=3mm maximum cancer core length are viewed as insignificant disease (figure 1)[28]. This is one way forward, to stratify the risk of individual lesions within the prostate, rather than the whole gland itself. The strongest application of this combined mapping biopsy and focal risk stratification technique is just that, a risk stratification map of the prostate gland (figure 2).

In addition, do we yet have at our disposal, imaging technology that can accurately localise cancer within the prostate? The development of such a tool would clearly revolutionise the diagnosis of prostate cancer. After all, prostate cancer stands alone as the sole solid organ malignancy where targeted biopsies based upon imaging are not standard practice. With regard to this situation Dr Patrick Walsh stated in 2008, "To the young people here, if you want to make a substantial contribution to medicine for this decade and maybe for the century, address yourself to the problem of imaging of cancer within the prostate gland"[30]. This is one of the fastest growing fields in prostate cancer and we have undeniably made great strides here.

We know that multiparametric MRI (mpMRI) can show discrete lesions within the prostate (figure 3) and that its negative predictive value (NPV) of is excellent, especially for significant disease[31]. Studies have compared mpMRI against examination of whole mount prostate specimens. For example, Villiers et al demonstrated a sensitivity, specificity, positive and negative predictive value of 77%, 91%, 86% and 85% for tumour foci of >0.2mL, and 90%, 88%, 77% and 95% for tumour foci of >0.5mL respectively when dynamic contrast enhancement is added to the MRI sequence protocol[32]. In an update from this group, sensitivity and specificity of 86% and 94% was reported for >0.5mL tumours[33]. Such findings are replicated in the systematic review by Futterer et al which found that mpMRI had detected clinically significant disease in 44% to 87% of men and had a negative predictive value of 63% to 98% where prostate biopsy or whole mount prostatectomy specimens were used as the reference standard[31]. It is not a perfect diagnostic test as it misses some high volume Gleason 6 or low volume Gleason 7 and very rarely higher grade disease[34]. Compared to our current standard of care upon which we make treatment decisions and which is 30-50% inaccurate, it is substantially better[28].

Studies have also compared the diagnostic accuracy of mpMRI against transperineal template mapping biopsy. This study design is particularly useful, as they so not apply a selection bias to the population. One example is Arumainayagam et al in 2013. They showed, as we know, that for the detection of any cancer mpMRI is a poor test with a NPV of between 60% and 63%[35]. However, when thresholds of histological risk are applied the results are excellent. For Gleason >/=3+4 disease and/or a maximum cancer core length >/=4mm the NPV was between 85% and 90%[35]. For Gleason >/=4+3 and/or a maximum cancer core length of >/=6mm the NPV was 93% to 97%[35]. Naturally these levels of risk must be applied to an individual patient, their expectations and what level of risk they are willing to accept. Similar studies from numerous centres have demonstrated similar results[36-41]. However, not wishing to rest on the evidence we have already, the PICTURE[42] and PROMIS[43] trials are set to report in the near future.

Reason 3 – 'Focal therapy 'treats' men who don't need treatment.'

This is not entirely accurate nor does it apply to focal therapy alone. A systematic review from 2014 found 2350 cases of localised prostate cancer in 30 studies, which were treated with focal therapy[44]. Gleason score was reported in 13 studies and PSA was reported in 11[44]. According to the D'Amico risk classification[45], approximately half of cases treated had intermediate or high risk disease[44]. Our group are building on this. In the prospective, investigator led INDEX trial, evaluating the efficacy of high intensity focussed ultrasound in the treatment of localised prostate cancer, we are now no longer including men with low volume Gleason 6 low risk disease[46]. The patients are free to elect for radical options but they will be excluded from undergoing focal therapy under our care. Additionally, although overtreatment of men with low risk disease with radical prostatectomy disease is falling, it still occurs[47]. Likewise, this occurrence is also seen, and more commonly so, with radical radiotherapy[48]. Indeed between 2004 and 2007 58% of men were treated with radical radiotherapy in comparison to less than 10% by active surveillance or watchful waiting[48].

Reason 4 – 'For men who need treatment, radical therapy is effective so men and their physicians have to just accept the side effects.'

This argument may sound familiar. The urological community experienced a similar reaction to the introduction of partial nephrectomy. Some argued that the patients would cope less well after partial nephrectomy, as they would fear a higher risk of recurrence despite the reduction in inevitable side effects of radical nephrectomy. This was tested and shown to be untrue[49,50]. This position was also seen with breast cancer but once again, these concerns appear to have been unfounded[51].

We cannot solely act on our patients' behalf in the out-dated paternalistic model of medicine. Men with prostate cancer are able and willing to make trade-offs when it comes to their treatment. We know that men are not willing to accept any side effect unless they receive a certain amount of life expectancy in return. A discrete choice experiment in 2012 demonstrated this quite elegantly. The authors found

that if you give a man severe urinary blockage, bowel symptoms or urinary leakage, he will want around two years of life in return beyond a typical 12 years of life without having treatment[52]. If you render him impotent he will want four to six months of life in return[52]. As the authors of the discrete choice experiment stated, this "underlines the need to inform patients of long-term consequences and incorporate patient preferences into treatment decisions.[52]"

Reason 5 – 'Focal therapy has no better functional outcomes than modern radical surgery.'

There are two critical parts to this statement. Firstly, what does one mean by "modern radical surgery"? Secondly, does this 'modern' approach benefit patients in terms of their functional outcome? Function outcomes being erectile function and urinary incontinence and with radiotherapy, rectal toxicity.

In regard to the first question, as things currently stand the robotic-assisted laparoscopic prostatectomy (RALP) might be regarded as the modern approach for the surgical management of localised prostate cancer. It has clearly replaced the open radical prostatectomy as the treatment of choice. The intraoperative blood loss and inpatient stay is demonstrably reduced with RALP[53], as is the immediate surgical morbidity[54]. However, there are many studies, some long term, reporting on the functional outcomes of prostatectomy and these have reported modest results which have been summarised in two pertinent systematic reviews. Firstly, Ficarra et al published systematic review of 51 articles in 2012 demonstrating 12 month 'no pad' incontinence rates of 4% to 31%, or 'no pad or safety pad' incontinence rates of 8% to 11%[55]. Likewise, that group also performed a systematic review of potency following RALP. After analysing 31 studies they found 12 to 24 month potency rates varied from 54% to 90% and from 63% to 94% respectively[56].

However, perhaps there were issues with user experience in these results. We know that there is a significant learning curve associated with prostatectomy[57-58] and perhaps the results from the most experienced centres are better. Carlsson et al

reported on functional outcomes of 1280 men 18 months following surgery[59]. Using patient-related outcome measures, they demonstrated surgeon heterogeneity for continence, but not for sexual function[59]. However, the overall functional outcomes still comparable to the above studies with 18 month continence and potency rates of 85% and 19% respectively[59].

Of course, the discerning eye will have noticed that these studies report on radical prostatectomy rather than purely RALP. However, purely in terms of functional outcomes, the evidence that RALP bears advantages over open prostatectomy is wanting[60-62]. A systematic review by Finkelstein et al in 2010 found no convincing evidence that RALP offered a functional outcome advantage over open prostatectomy[60]. Haglind et al compared 778 open prostatectomies with 1847 RALPs[61]. 56% of men who had open prostatectomies were not pad or leak free at 12 months post surgery compared to 57% of those who underwent a RALP[61]. This difference was not significant. The RALP fared marginally better in sexual function however with 30% being potent compared with 25% of men who had an open prostatectomy[61]. Likewise, Jackson et al found no significant difference in the functional outcomes at 10 years between open prostatectomy and RALP[61]. Short-term results have demonstrated an improvement with RALP over open prostatectomy[63]. However, as things currently stand the evidence that modern surgery is better than open surgery in terms of functional outcomes is poor in itself.

The functional outcomes of focal therapy compare rather well. Valerio et al in a systematic review found that in the studies using validated patient-related outcome measures that leak-free incontinence rates were 83% to 100%, the pad free incontinence rates were 95% to 100% and that 53% to 100% of men were able to maintain an erection sufficient for penetration without or without the use of a PDE5-Inhibitor[64]. Rectal fistula rates were reported in between 0% and 1% of cases and usually occurred early in the learning curve[64]. Similarly, Yap et al found that although there is a significant fall in potency at one and three months post surgery, after that time there is no difference between the pre and postoperative degree of potency following focal HIFU[65].

Long-term functional follow-up is still needed but from the evidence that is available to us, it cannot be stated the functional outcomes of modern radical surgery are the same as focal therapy.

Reason 6 – 'Treating less than the whole prostate risks leaving cancer behind, so you're risking men's lives.'

Once again, this is an argument we should all already be familiar with. When the nerve sparing prostatectomy was developed, sceptics, with an amusing turn of phrase, declared, "The procedure is cancer-sparing surgery[66]." Some contemporaries felt at that time, that total prostatectomy should remain the optimal treatment for patients with localised cancer of the prostate[67]. It was through the meticulous work of Patrick Walsh in Johns Hopkins that it was demonstrated that nerve-sparing surgery was oncologically safe. In deed, based on this series of 100 cases, an entire treatment modality shifted internationally[68]. We saw the same arguments regarding nephron-sparing surgery. For example, Wunderlich et al in 1999 stated that the major disadvantage of nephron-sparing surgery for renal cell carcinoma is the risk of local recurrence[69]. Interestingly, this paper noted that in 90% of cases of renal cell carcinoma, the disease was bilateral. We doubt that one would advocate bilateral radical nephrectomy even if the only concern were the risk of out of field disease recurrence. Not to mention that these fears were unfounded as was touched upon earlier[10].

Are these same concerns valid for focal therapy? The evidence available to us at this time suggests perhaps not. Bahn et al demonstrated in the follow-up of 73 men who had undergone cryotherapy for localised disease, that cancer control in the treated side of the gland was good[70]. In almost all men, based on year-on-year TRUS and targeted biopsy there was no recurrence of disease in the treated side[70]. Around 40% of men would however, have biopsy positive disease at five years post surgery[70]. Likewise, Rouget et al reported on 191 patients who were treated for localised prostate cancer with high-intensity focussed ultrasound. At a mean follow-up of 55·5 months the metastatic-free survival was 97·4%[71]. When one looks at the existing literature as a whole, then a similar picture emerges. In studies reporting

short to medium term follow-up, that on postoperative biopsy, the rates of any cancer being detected are between 3.7% and 23%, which falls to 0% to 17% when adjusted for clinical significance[64]. 0% to 33% require further whole gland therapy and as the follow-up lacks longevity the rates of metastasis or death from disease are 0% to 0.3%[44]. We argue that this evidence shows good disease control in the short to medium term.

Reason 7 – 'There is no data from randomised controlled trials'

No there is not. In fact there is little in the way of comparative data at all. But one cannot ignore that our advocacy of the efficacy of radical prostatectomy is based on a single comparative study of radical prostatectomy versus no early intervention at all[71] even though a subsequent RCT showed no overall survival benefit in treatment compared to watchful waiting[72]. This is not a problem solely experienced by focal therapy, or even urology in general. The extent of the problems experienced in surgical comparative research cannot be understated. As we can see from the examples above, surgeons think they know best and patients usually want to have choice in their treatment. Our treatment of renal cell carcinoma once again can provide a pertinent example. In 2010 the European Association of Urology published its guidelines for treating localised renal cell carcinoma. They stated, "Patients with low-stage RCC (T1) should undergo nephron sparing surgery. Radical nephrectomy is no longer the gold standard of treatment in these cases[73]." These were published before the EORTC randomised controlled trial comparing the oncological outcomes of the two techniques reported[74]. As a result the trial investigators lost equipoise. As they stated three years previously when reporting on complications of the two techniques, "The oncologic results are eagerly awaited to *confirm* that NSS is an acceptable approach for small asymptomatic RCCs." It was revealing that they wished to confirm the disease control outcomes and not discover it relative to nephrectomy.

Can we improve on our similar predicament in prostate cancer? As things stand we have had some successes. However, the number of failures outweighs these. Invariably, our trials have failed either due to low patient recruitment, or lack of

physician equipoise[75]. We can, and must, keep making attempts to design trials that will gather good comparative data. However, rejecting focal therapy due to an issue that plagues all of surgery is not consistent with changes in practice that have been advocated and made based on non-comparative data.

Conclusions

Focal therapy is the next stage in surgical innovation for treating localised prostate cancer. As a paradigm shift, it reflects the biology of the disease. Prostate cancer is multifocal in the majority of cases. However, the biology of the disease makes not treating Gleason 6 lesions and therefore parts of the prostate a legitimate strategy. We do have the tools to accurately locate disease within the prostate, but these are not 100% accurate. Likewise we have the tools to treat focally and whilst these are not 100% effective, medium term outcomes demonstrate effectiveness with remarkably lower side-effect rates. Finally, we must continue to strive to develop large, multi-centre long term studies.

Funding Source

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Figure and table legends

Figure 1: The University College London histological risk stratification system.

Figure 2: An example of a histological risk map derived from a template mapping biopsy; in this case using modified Barzell zones.

Figure 3: An example of mpMRI demonstrating discrete identifiable lesions within the gland. The lesion identified by the arrow is clearly visible in T2 weighted, ADC and DCE sequences.

Table 1: A summary of the arguments for and against focal therapy in localised prostate cancer