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Platinum Opinion

Modern Imaging in Prostate Cancer: Do We Treat Patients, or Their Scans?

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Why do we image patients with prostate cancer? It is for better characterisation of their disease, which leads to better treatment decisions and, in turn, to better outcomes. There is no doubt that new imaging techniques (including magnetic resonance imaging [MRI] and positron emission tomography [PET] with targeted tracers) are more sensitive than conventional imaging in prostate cancer, and reveal sites of disease that we might never have seen with conventional imaging [1,2]. As a result, modern imaging results in stage migration and a natural temptation to change clinical management. An example is the use of MRI in men under active surveillance for low-risk prostate cancer, which results in higher rates of definitive intervention even in the absence of biopsy upgrading [3]. We already have data showing that advanced imaging in the context of biochemical recurrence after radical prostatectomy leads to a change in clinical decision-making when compared with conventional imaging [4], but will this translate into better survival?

It is often assumed that prostate cancer should be treated in the same way as its equivalent in the era before modern imaging, but is that right? Should all patients with metastases visible on PET only be treated in the same way as those presenting with M1 disease detected by bone scan only? Or are there some patients in this category who will still benefit from local treatment, even if they have multiple (say >3) bone metastases on their PET scan? If the latter is true, then denying such patients local radiotherapy or surgery would be undertreating them. The MRC STAMPEDE trial showed that patients with three or fewer bone metas-

tases (defined on a conventional bone scan) still benefited from local radiotherapy, even with a more gentle schedule than is usual for primary curative therapy [5]. The Inter-group study in locally advanced disease was one that showed a clear benefit from local curative radiotherapy when added to ADT for patients who had clinical M0 disease but were staged purely conventionally in an era long before PET and even MRI were widely available [6]. Were these patients staged today using MRI and PET, some of them would be classified as having M1 disease. Was it therefore wrong to treat them with local radiotherapy? Conversely, patients with very early PET-defined metastatic disease could derive even more benefit from intensified systemic therapy than those with more bone scan-only M1 disease [4,5]. In the context of biochemical recurrence after radical prostatectomy, PET-defined small-volume metastases not seen on conventional bone scans may well exclude patients from local salvage radiotherapy (SRT). The recent EMPIRE-1 study excluded patients with extrapelvic or skeletal disease on PET from SRT [4]. Indeed, biochemical outcomes were better in the group who were PET-negative and who received SRT, but this does not prove that patients with PET-defined small-volume M1 disease would not have benefited at all from SRT, even if it is conceivable that they would have done less well.

Pandora's box is open: we cannot ignore modern imaging techniques and continue (re)staging and treating disease as we did in the era of conventional imaging. Instead, we must learn how to properly interpret modern

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imaging and how to treat patients, with an understanding of what that treatment achieves in terms of clinical outcomes such as overall survival, disease recurrence, and quality of life. This will only be achieved with sufficiently large studies of patients followed up long-term, even if such studies are observational, as it may be hard to randomise patients in this context. Failure to “grasp the nettle” of conducting these studies will result in major changes in treatment practice without any proven efficacy, expose patients to the risks of overtreatment and undertreatment, and increase side effects, costs, and the use of resources. It should be our responsibility as practitioners to conduct such studies and not simply to jump on the bandwagon afforded by these new and attractive tools.

The dilemmas introduced by modern imaging are not confined to metastatic disease. For example, large numbers of patients who are staged today using MRI of the prostate are categorised as having locally advanced disease, sometimes on the basis of quite small and subtle radiological abnormalities. It is obvious that such patients are not the same as those who participated in the Intergroup and other studies who were categorised as having locally advanced disease, principally on the basis of clinical examination [6]. Comparisons of outcomes in MRI-staged locally advanced disease with populations of patients treated on the basis of conventional imaging alone are irrevocably flawed, and even simple measurement of outcomes in a mixed population, some of whom have had modern imaging, are meaningless. For the individual patient with “imaging-defined locally advanced disease”, we simply do not know whether 3 years of ADT plus radical radiotherapy (or indeed combined surgery and radiotherapy) is the optimum treatment, or whether for some it is overtreatment. MRI is also affecting grade: MRI-targeted biopsies are more likely to identify intermediate- and high-risk cancers, which undermines the value of risk classifications such as the D’Amico scheme that are based largely on sextant biopsies.

From a cancer control and public health standpoint, the consequences are also substantial. Evaluation of survival trends in populations in which modern imaging has resulted in a stage shift and/or leadtime bias will be misleading at best, and could be damaging if resource allocation is based on such data. Could a modification to the staging classification help to ameliorate this bias? Both the Union for International Cancer Control (UICC) and American Joint Committee on Cancer versions of the TNM staging classification [7,8] currently assign T category without using information from imaging, although clinicians are increasingly ignoring this and recording T categories on the basis of MRI staging and M categories on the basis of MRI or PET imaging. Arguably, this is a problem across the entire spectrum of cancer types, but we would maintain that the natural history of prostate cancer as understood today gives a particular urgency to resolving the issue for this disease type. For locally advanced disease, the solution could be simple; introducing a specific category of T3 disease, defined as “evidence of primary disease outside the prostate gland seen on MRI or PET only” would capture those patients with clinical T1/2 disease but radiological evidence of more extensive disease. It would also encompass the increasing number of patients for whom digital rectal examination is simply not performed, as the patient proceeds straight to MRI. This is not a perfect solution and

the terminology would need to be agreed. For example, the prefix “mi” has been suggested as a way of defining disease stage based on PET molecular imaging [9]. The UICC are reluctant to change the TNM classification in the absence of evidence, and we support this stance, but would argue that the evidence pertaining to stage migration and imaging in prostate cancer is now too strong to accept the current situation. An imaging “prefix” to the TNM category, while imperfect, would be an improvement on the current situation. For nodal and distant metastases, a similar category might be added; this might need more debate, but we would advocate for making a distinction between disease visible on MRI or PET in comparison to conventional X-ray, bone scan, and computed tomography. There is a case for a further separation of MRI- and PET-defined categories, and academic centres, at least, should record data with a granularity that allows such distinctions to be made, but this might be too detailed for a general classification such as the TNM scheme. Whatever the solution, we believe that the next iteration of the TNM classification should at least recognise the problem in some way, and in a manner that will suffice until we have the long-term data that will help us to better understand the natural history of disease defined by more sensitive imaging such as MRI and especially PET. We look forward to working with the UICC in anticipation of their 9th edition of the TNM classification. Novel imaging technology has much to teach us about the biology of prostate cancer. The entire “oligometastasis” field is greatly aided by prostate-specific membrane antigen PET imaging, and novel imaging is ready to challenge some old Halstedian dogmas [10]. It is up to us to further advance the field by applying new imaging, with rigorous recording of data and outcomes, and to translate these findings into patient benefit.

Conflicts of interest: Malcolm D. Mason is a company consultant for Ellipses Pharma and Oncotherics, and has received payments for membership of data monitoring committees for Endocyte and for Clovis. Theodor van der Kwast has received research support from Google Inc. Nicolas Mottet is a company consultant for Janssen, GE, BMS, Sanofi, and Astellas; has received speaker honoraria from Astellas, Pierre Fabre, Steba, Janssen, and Ferring; and has received fellowships and travel grants from Astellas, Ipsen, Sanofi, Janssen, and Roche. Olivier Rouvière has received a speaker honorarium from EDAP-TMS and travel grants and research support from Philips, and has participated in clinical trials run by EDAP-TMS and Vermon. Erik Briens has received grants and research support from Ipsen, the European Association of Urology, and Bayer; is an ex officio board member for Europa UOMO; is an ethics committee and advisory group member for REQUITE; is a patient advisory board member for PAGMI; and is a member of SCA and EMA PCWP. Philip Cornford is a company consultant for Astellas, Ipsen, and Ferring; has received company speaker honoraria from Astellas, Janssen, Ipsen, and Pfizer; has participated in trials run by Ferring; and has received fellowships and travel grants from Astellas and Janssen. Maria De Santis is a company consultant for Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Eisai Inc., ESSA, Ferring, GSK, Incyte, Ipsen, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SeaGen, Shionogi, Synthon, Takeda, Teva, OncoGenex, and Sandoz; receives speaker honoraria from Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Ferring, GSK, Ipsen, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, Synthon, and Takeda; participates in trials run by the Technical University Munich,

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