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European Association of Urology

## Letter to the Editor

**Re: Gaëtan Devos, Gert De Meerleer, Steven Joniau. Have We Entered the Era of Imaging Before Salvage Treatment for Recurrent Prostate Cancer? Eur Urol 2019;76:265–7**

We read with interest the paper by Devos et al. [1] warning against “blind” salvage therapies such as salvage lymph node dissection and salvage radiotherapy (sRT) in prostate cancer patients with biochemical recurrence (BCR) following primary treatment. While this might hold true for patients who experience recurrence after primary RT, the authors actually only report on 78 patients who had BCR after radical prostatectomy (RP). We would argue that for the majority of those patients, “blind” sRT remains the only evidence-based and potentially curative treatment option that should be initiated as early as possible.

First, sRT, even when performed “blind”, is incredibly effective in the vast majority of patients. This was already evident in older adjuvant RT trials (eg, SWOG S8794, EORTC 22911, ARO 96-02) [2] and more recently confirmed in the GETUG-AFU 16, NRG/RTOG 9601, and NRG/RTOG 0534 SPPORT trials [3–5]. Those trials reported long-term disease control rates >70%, even in their respective control arms (ie, “blind” sRT alone).

Interestingly, these data are entirely consistent with literature results for prostate-specific membrane antigen (PSMA)—and indeed choline—positron emission tomography (PET), which has repeatedly shown locoregional disease in approximately 70–75% of patients, numbers that could potentially be prevented by early pelvic sRT [6]. The authors’ own data are a case in point, with 73.1% of cases having local or pelvic disease, even at a high median prostate-specific antigen (PSA) level of 2.6  $\mu\text{g/l}$  [1].

However, sRT has a certain “therapeutic window” and yields the best outcomes when initiated at PSA levels below 0.2 or even 0.1  $\mu\text{g/l}$  [7]. Conversely, PSMA PET/computed tomography (CT) has a clear “diagnostic window” as its sensitivity is still limited at PSA values below 0.2 or even 0.5  $\mu\text{g/l}$  [8]. Thus, while waiting for a positive finding on imaging, we are potentially denying patients their final chance of a cure. Indeed, patients with negative PSMA imaging have an exceptionally high treatment response to

sRT and this treatment should certainly not be withheld from them [9].

Moreover, how sure are we that what we see on modern imaging is real? Most of the PET studies thankfully used an index test (pathology, PSA drop after treatment, growth on subsequent scan, confirmation via another imaging modality), but this was not always applied very stringently and consisted of actual pathology in less than half of the studies [6]. Furthermore, in the few studies with pathologic confirmation, PSMA PET/CT has specificity of 85–90%, so more than one in ten lesions is not prostate cancer [6,10]. In fact, we have probably underestimated false-positive PSMA scans. Our knowledge of normal versus abnormal physiological distribution and of confounding PSMA uptake in nonprostatic pathologies (eg, celiac ganglion, Paget’s bone disease, reactive lymph nodes, lung cancer, renal cell cancer) is at a relatively early stage [11].

In conclusion, fear of “blind” sRT is totally unfounded, since postprostatectomy RT is a highly focused treatment that is very effective and well tolerated [12]. While imaging studies have shown changes in management for some patients, it has never been proven that imaging use alters clinical outcomes [13]. Randomized trials of PSMA PET/CT using clinically meaningful endpoints are urgently warranted.

Postoperative imaging should be considered for patients who are estimated to have a higher risk of harboring measurable disease (eg, PSA >0.5  $\mu\text{g/l}$  or persistent or rapidly rising PSA). For all other patients, the risk of depriving them of a potentially curative option is far greater than the risk of missing a new lesion. Contrary to what the authors claim, the latest EAU-ESTRO-ESUR-SIOG guidelines “strongly” recommend to “treat patients with a PSA rise from the undetectable range with sRT”, and not withhold or defer sRT [14].

**Conflicts of interest:** The authors have nothing to disclose.

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Piet R. Dirix<sup>a,\*</sup>  
 Alan Dal Pra<sup>b</sup>  
 Thomas Wiegel<sup>c</sup>

<sup>a</sup>Radiation Oncology, Iridium Cancer Network, Antwerp, Belgium  
<sup>b</sup>Department of Radiation Oncology, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL, USA  
<sup>c</sup>Department for Radiation Oncology, University Hospital Ulm, Ulm, Germany

\*Corresponding author. Radiation Oncology, Iridium Cancer Network, Oosterveldlaan 24, Antwerp 2610, Belgium. Tel. +32 3 4433737. E-mail address: [piet.dirix@gza.be](mailto:piet.dirix@gza.be) (P.R. Dirix).

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