Editorial

Oligometastatic prostate cancer: is it worth targeting the tip of the iceberg?

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Until recently, the only routinely available imaging techniques of prostate cancer were computed tomography (CT) scan ± contrast, magnetic resonance imaging (MRI) and a standard bone scan. The increasing use of modern imaging techniques such as positron emission tomography-computed tomography (PET-CT) with tumour-specific radiotracers [Choline, Fluciclovine or prostate-specific membrane antigen (PSMA) ligand], and, increasingly, whole-body MRI with diffusion-weighted imaging (WB MRI-DWI), means that oligometastases in prostate cancer are commonly discovered before any radical treatment or once the prostate specific antigen (PSA) has risen following radical treatment. Lesions discovered on imaging represented well-established disease for which only palliative therapy could be considered appropriate. These recent advances in imaging have led to the emergence of the oligometastatic prostate cancer (OPC) term, and re-examination of the therapeutic propositions appropriate in this situation. Nevertheless, the OPC definition encompasses a range of scenarios, in which one, three, five or as many as ten metastatic sites may have been identified (1). The definition will continue to evolve with the increasing use of new imaging techniques, as will the definition of "the right treatment at the right time for the right patient", and the recent consensus statement of the EORTC imaging group highlights the need for more clinical trials employing such imaging to evaluate the benefits of metastasis-directed therapies (2).

Modern imaging methods can help to reveal small metastatic lesions that were invisible to conventional imaging. The sensitivity and specificity of currently available modern imaging techniques are illustrated in *Table 1*. In addition to its excellent specificity, PSMA-ligand PET-CT is highly sensitive, even in scenarios where the PSA has increased very little. A positive ^{68}Ga/^{18}F-PSMA PET-CT scan was able to detect potential sites of recurrence in a median 51.5% of patients, even when the PSA was less than 1.0 ng/mL, in 74% of patients with a PSA of between 1.0 and 2.0 ng/mL, and 90.5% of patients in whom the PSA was higher than 2.0 ng/mL review of ^{11}C/^{18}F choline and ^{18}F-fluciclovine data commonly showed lower detection rates for each respective PSA cohort (9). Indeed, it is this performance that has led to the emergence of the oligometastatic term and the consideration of new therapeutic strategies in these situations. There remains, however, the problem of access to these modern imaging techniques. The necessary radiopharmaceuticals, and the WB MRI-DWI, are not equally available in all countries, even within Europe. The short half-life of ^{68}Ga means that ^{68}Ga-PSMA cannot be transported far, so the technique requires costly local gallium generators, to circumvent the problem that such isotope markers have lower yields by the end of their half-life. These logistical difficulties mean that the use of ^{68}Ga-PSMA is in practice limited to PET centers with radiochemistry facilities. This deficit means that a consensus definition of OPC is still open for debate.

Prostate cancer is radiosensitive, and the promising results obtained with radioimmunotherapy (RIT) and targeted PSMA radio-ligand therapy (RLT) in multi-metastatic patients means that these techniques seem likely

Table 1 Meta-analyses of the sensitivity and specificity of Choline, Fluciclovine and PSMA PET-CT and bone metastases with F-Na PET-CT and WB MRI-DWI

Meta-analyses	No of studies	No of patients	Sensitivity per patient (95% CI), %	Specificity per patient (95% CI), %
CHOLINE				
Fanti *et al.* (3)	12	1,270	89.0 (83.0–93.0)	89.0 (73.0–96.0)
FLUCICLOVINE				
Ren *et al.* (4)	6	251	87.0 (80.0–92.0)	66.0 (56.0–75.0)
PSMA-ligand				
Perera *et al.* (5)	16	1,309	86.0 (37.0–98.0)	86.0 (3.0–100.0)
von Eyben *et al.* (6)	9	983	87.0	93.0
Bone mets; F-Na				
Tateishi *et al.* (7)	11	425	96.2 (93.5–98.9)	98.5 (97.0–100.0)
Bone mets; WB MRI-DWI				
Liu *et al.* (8)	32	1,507	95.0 (90.0–97.0)	92.0 (88.0–95.0)

CI, confidence interval; PSMA, prostate-specific membrane antigen; PET-CT, positron emission tomography-computed tomography; MRI-DMI, magnetic resonance imaging with diffusion-weighted imaging.

to find a place in practice, either as a first-line approach, or as an important additional treatment to complement already-established protocols (10-13). All recent published studies have recruited multi-metastatic patients, but it has also been observed that the large tumor mass in these patients limits the long-term effectiveness of this therapy and increased toxicity has also been reported. Both RIT and RLT targeting PSMA are particularly adapted to scenarios where disease is limited, and there is a considerable interest in increasing access to modern imaging methods capable of detecting it. Modern imaging techniques such as PET-CT PSMA targeting, either with PSMA ligand or immuno PET-CT, also open the possibility of theranostic approaches.

In a trial published after the appearance of the EORTC consensus, prostate irradiation combined with androgen depriving therapy (ADT) and chemotherapy was shown to prolong overall survival in newly presented OPC patients with low tumor burden (14). Oligometastatic stage was defined on conventional imaging techniques (CT scan, total bone scan), and radiotherapy was limited to the primary tumor. The role of modern imaging techniques in this particular setting remains moot. Should patients with apparent OPC on conventional imaging, but in whom polymetastatic disease is discovered using modern imaging techniques, still be offered prostate cancer radiotherapy? Should treatment be offered for both the prostate and the oligometastases in this category of patients? The currently varying definition of oligometastic disease is an obvious obstacle to obtaining clear responses to such questions. The main objective of future studies in oligometastatic patients will be to discover whether metastasis-directed treatments, such as surgery or radiotherapy, prolong overall survival or time to castration resistance, as recommended by the ICECAP working group (15). For example, the GETUG 36 study will randomize newly-diagnosed oligometastatic patients to conventional treatment (ADT + chemotherapy + prostate cancer radiotherapy) with or without SBRT to oligometastases, as defined on modern imaging (16).

Oligometastases in pelvic lymph nodes might represent a potentially curable stage since lymph node dissection showed a small proportion of long-term survivors in *de novo* or relapsing pelvic oligometastases. Modern imaging techniques should help to define whether surgery radiotherapy or a combination of both is the best strategy for treating such pelvic lymph nodes. For example, pelvic lymph node dissection is obviously more difficult to perform when oligometastic lymph nodes measure only a few millimeters, or when they are located in close relation to large blood vessels. Should only the detected lymph nodes be treated with SBRT, or should this be combined with high doses to the lymph nodes using elective pelvic node irradiation? Retrospective studies suggest that an elective approach might be superior to more selective radiotherapy (17). The oligopelvis GETUG P07 study

Table 2 Selected ongoing studies in OPC

NCT accession number	Imaging modality	Number of met	ADT	HS/HR	Treatment type	Start date	Institution
NCT02563691	Conventional staging	LN, bone ≤5	Intermittent	HS *de novo*	SBRT	2015	Sunnybrook
NCT02716974	Conventional staging	LN, bone ≤5	Intermittent + chemo	HS *de novo*	Surgery + SBRT	2016	Johns Hopkins
NCT03569241	FCH PSMA or FACBC PET-CT	≤3 lesions	Yes, 6 months	HS relapse	conv RT ± MDT	2018	U of Ghent
NCT02680587	DCFPyL-PET/MRI or -PT/CT	≤3 lesions	NR	HS relapse	Observation *vs.* SBRT	2016	Johns Hopkins
NCT02192788	FCH PET-CT	LN, Bone	NR	HS relapse	SBRT	2014	Hospital Provincial de Castellon
NCT02264379	Acetate PET, PET-PSMA, NaF-PET	LN, bone	No	HS relapse	SBRT/conv RT	2016	Technische Universität Dresden
NCT00544830	PET or ProstaScint scan	≤5 lesions	Yes, 36 weeks	HS relapse	HFRT	2016	City of Hope
NCT02685397	Standard	≤5 lesions	Yes, Enzalutamide	HR relapse	HT ± SBRT	2016	Jewish General Hospital
NCT01859221	NR	NR	Yes	HS/HR	SBRT, HFRT protons	2016	U of Florida
NCT02484339	Standard	≤5 bone	Continuous	HR relapse	SBRT ± ^{223}Ra	2015	U Freiburg
NCT03630666	FCH or PSMA PET-CT	≤5, LN pelvis	Yes, 6 months	HS	Elective pelvic irradiation	2018	U Nantes
NCT03795207	FCH or PSMA PET-CT	≤5, bone or LN outside pelvis	No	HS	SBRT ± durvalumab	2018	U Nantes

LN, lymph nodes; HS, hormone-sensitive; HR, hormone-resistant; HT, hormone therapy; HFRT, hypofractionated radiotherapy; SBRT, stereotactic body radiotherapy; MDT, metastasis-directed therapy; NR, not reported; OPC, oligometastatic prostate cancer; ADT, androgen depriving therapy.

combined 6-month ADT with high dose elective pelvic nodes irradiation (18). No short-term toxicity was reported, but long-term efficacy and tolerance has yet to be reported (19). The Oligopelvis 2 GETUG P12 phase 3 trial, which will randomize 6-month ADT with or without elective salvage pelvic lymph node irradiation (NCT03630666) and several other clinical trials (*Table 2*) should help to resolve these questions.

An oligometastatic "stage" probably does not exist. It is likely instead that the scenario merely reflects the current failure to visualize the full extent of the metastatic spread. Whatever the radiotracer employed, we will almost certainly never be able to localize sub-millimetric metastases. It is therefore highly unlikely that SBRT would be able to completely eradicate all tumor cells. Until now, strategies combining SBRT to oligometastases and systemic therapy such as enzalutamide have been based only on spatial cooperation. However, a few tumor models have shown that SBRT was able to trigger a tumor-oriented immune response, that enabled the destruction of unirradiated metastatic sites—the so-called abscopal effect (20). We currently have no data on this effect in prostate cancer, but Sipuleucel T, an autologous vaccine approved for treatment of men with asymptomatic or

minimally symptomatic castrate-resistant metastatic prostate cancer, has been shown to increase survival (21), which suggests that a tumor-targeting immune response may be solicited in prostate cancer. And while trials of ipilimumab have not improved overall survival in prostate cancer, it nevertheless has been shown to impact the natural course of castration resistant prostate cancer in some patients (22). Such potentially synergistic combinations of immunotherapy and SBRT in OPC patients are obviously ripe for study. The POSTCARD GETUG P13 trial, a randomized phase 2 study of a combination of SBRT with the anti-PD-L1 antibody durvalumab is one example of the kind of trial that is now necessary to resolve the uncertainties around oligometastatic disease. The booming number of immune targeting strategies will need to be specifically evaluated in OPC, especially when combined with radiotherapy.

Modern imaging techniques mean that more and more of the tip of the iceberg of metastatic prostate disease is visible above the waterline. The task of researchers in the field is now to show that this new-found recognition may enable effective interventions in metastatic prostate cancer by combining systemic therapies and treatments targeting the newly-visible disease.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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