Editorial

Oligometastatic disease in prostate cancer, a continuously changing paradigm: patient selection and treatment strategy

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The recent publication of the results of a relatively large cohort of patients treated with stereotactic body radiation therapy (SBRT) at the Mayo Clinic for oligometastatic prostate cancer (1) has to be considered as another significant step toward the assessment of the potential of radiation therapy in the optimal management of these "niche" patients.

Despite the retrospective nature of the study, the authors reported promising results in a subset of 66 castration-resistant patients with 81 metastatic lesions (predominantly skeletal) mostly treated in a single fraction. In addition, a dose effect was suggested with a much better outcome for patients treated to ≥18 Gy, not exhibiting any local failure at a median follow-up of 16 months. These results provide us with the opportunity to contribute to the ongoing discussion regarding the rapidly evolving role of radiation therapy in this emerging context.

Firstly, why this interest in prostate cancer metastatic disease? Among several reasons, it is important to underline the increasing incidence in recent years, as observed by Weiner *et al*. (2), which analyzed 767,550 prostate cancer patients diagnosed from 2004 to 2013 in 1,089 US hospitals. The incidence of metastatic disease has increased in all age groups by 72%, with the largest increase (92%) in men aged 55–69, those who should benefit most from prostate cancer screening. The causes of this increase are the substantial reduction in PSA screening recommended by US Preventive Services Task Force, in 2008 and 2012 (3), and the development of more refined diagnostic capabilities.

Moreover, in recent years active monitoring is being increasingly prescribed. In the October 2016 issue of *The New England Journal of Medicine*, Hamdy *et al*. presented the 10-year results of the first study comparing active monitoring, surgery and radical radiotherapy (4). A similar survival rate was observed among the more than 1,600 randomized patients in the three arms, although a trend of increasing mortality was registered with active monitoring in the group of patients 65 years or older at diagnosis. Interestingly, the incidence of metastatic disease was found to be significantly higher in the active monitoring group. While radical surgery worsened subsequent quality of life, 5 years after treatment erectile dysfunction was similar in the monitoring and radiotherapy arms, with incontinence better in the radiotherapy arm (5). Notably, this important study suggests that, since monitoring is being increasingly used, we must consequently expect an increase in the number of metastatic patients, who are candidate to palliative systemic therapies (6).

The second reason for the growing focus on oligometastatic prostate cancer patients is the better knowledge of the concept of metastatic disease and its natural history. In 1995 the oligometastatic status was defined in an editorial published by *Journal of Clinical Oncology* (7). The authors, Hellman and Weichselbaum, stated that the process of cancer metastasis occurs along a continuum, from locally confined cancer to widely metastatic disease, opening the way towards the exploration of more radical (local and/or regional) therapies, including both surgery and radiation therapy, added in this phase, at the primary and metastatic sites (8).

Oligometastatic disease is generally defined as a limited number, up to 5, of metastases, localized in no more than

three organs. Recent clinical studies have shown that patients harboring oligometastatic disease are potentially curable with surgical resection and/or radiotherapy, but the biological properties that render them amenable to loco-regional therapy are not yet clear, making proper patient selection an increasingly critical factor. We are still in the early stages of a comprehension of the mechanism of progression from primary tumor to oligometastasis, and then to overt polymetastatic disease.

The group of Weichselbaum and Hellman has continued its research, focusing on the role of micro-RNAs involved in the development of metastatic disease. They have tried to understand the regulation of the process and observed a difference in progression between oligometastatic and polymetastatic disease, which could perhaps change the paradigm: micro-RNAs analyses of samples from oligo- and polymetastatic patients suggest that they are different biologic entities rather than discrete points in a continuous evolution; in other words, it seems that secondary lesions with oligometastatic phenotype originate from different tumor clones as compared to metastases with polymetastatic phenotype (9). However constant evolution (10) and self-seeding (11), as already demonstrated, complete the complex mechanism of multi-step metastatic cascade. Each step probably provides a bifurcation, leading to pronounced differences between oligo- and poly-metastatic cells. Thus, the metastatic phenotype is heterogeneous, and the three cohorts of oligometastatic patients (synchronous, metachronous and with induced secondary lesions after cytoreductive therapy) have different prognoses and may require different treatments (9). Micro-RNAs regulate epithelial-mesenchymal transition, formation of a pre-metastatic niche, tumor invasion, intravasation, distant vascular extravasation, adaptation of surviving tumor cells to the new microenvironment, proliferation with secondary tumor growth and angiogenesis. Thus, understanding the target genes may allow the development of targeted therapies. The process is very complex and far from being thoroughly understood; functional or mutational changes of single proteins involved in the processing of micro-RNAs can affect hundreds of down-stream genes. Oligometastatic patients presented some thirty differentially expressed oligo micro-RNAs relative to the polymetastatic cohort (12). Despite this complexity, micro-RNAs represent only part of the process. Being another potential target for therapeutic intervention, chemokine receptors such as CXCR7/RDC1 play an important role in prostate cancer metastases and progression (13). Thus, finding a highly efficient targeted therapy is a very difficult task, with no answer close at hand. In the short term, due to complexity and costs, genetic analysis is not a very feasible tool for patient selection.

The third reason is, importantly, the development of diagnostic capabilities, especially thanks to recent advances in nuclear medicine. In the last decade, several authors have demonstrated the role of 11 C and 18 F choline, which allow us to perform an earlier diagnosis of metastatic prostate cancer disease (14-17). Both sensitivity and specificity have increased with experience for the diagnosis of lymph-nodal relapses. Moreover, choline PET/CT has demonstrated higher specificity, positive predictive value and accuracy for bone metastases than bone scan (18). A recent meta-analysis of 12 studies with 1,055 patients (19) demonstrated that choline PET/CT has, in prostate cancer patients with biochemical recurrence, a pooled sensitivity and specificity of 85% and 88% respectively, in identifying the site of relapse, thus being the most useful diagnostic tool in patient selection, treatment planning and follow up to date (20).

The last, but not least significant reason is the increasingly high precision of radiotherapy delivery. Based on diagnostic and technical developments, radiation oncologists have tried to perform salvage treatments in patients with a limited number of metastases. The first published studies of highly precise stereotactic body radiotherapy, using ablative doses, demonstrated substantially improved outcomes in oligometastatic patients, when "radical" dose treatments are delivered (21).

In 2004, Singh and co-workers published an interesting study which posed the question of the potential role of radical treatments in prostate cancer bone metastasis (22).

The clinical evolution of metastatic disease in 369 prostate cancer patients with stage T1-T3aN0-NXM0 at diagnosis, treated with curative radiotherapy, was analyzed over a 10-year follow-up period. A total of 74 patients (20%) developed metastases and the 5- and 10-year overall survival in this group of patients was 58% and 27%, respectively. Patients with pelvic bone metastases fared worse when compared with those with vertebral metastases, and patients with ≤5 metastatic lesions exhibited superior survival rates, of 73% and 36% at 5 and 10 years, respectively, versus only 45% and 18%, in patients with more than five metastases (22). The authors reached the conclusion that patients with ≤5 metastatic sites achieved better survival rates and thus early diagnosis and aggressive treatment can improve long-term survival.

Recently, Schick *et al*. published a study analyzing 50

oligometastatic (1–4 metastases) prostate cancer patients. Metachronous metastases were dominant (43 patients), but in seven patients synchronous metastases were already evident at the initial diagnosis. The 3-year biochemical relapse-free survival was superior in patients with only one as compared with those who are with more than one metastasis: 66.5% *vs*. 36.4% (P=0.031). In addition, a normalized total dose >64 Gy to the metastatic sites was predictive of improved biochemical relapse-free survival (bRFS: 65% *vs*. 41.8%, P=0.005) (23).

In 2015, Ost published a systematic review of all studies of metastasis-directed therapy (MDT) with surgery and radiotherapy for oligometastatic PCa recurrence (24). Fifteen studies, published from 2008 to 2015, reported on 450 oligometastatic prostate cancer patients diagnosed with PET/CT, 66% of whom were treated with radiotherapy. The majority of these studies pertained to quite heterogeneous populations, with 78% of the oligometastatic patients being treated for lymph nodal recurrence, 21% for bone metastasis and only 1% for visceral metastasis. The meta-analysis demonstrated that, overall, half of the patients were progression free 1–3 years after salvage therapy, with low toxicities.

In a subsequent analysis Ost presented the multi-institutional results obtained in patients treated with stereotactic radiotherapy (SBRT) only (25). In patients with up to three metastases at PET/CT a median distant progression free survival of 21 months and an actuarial 3 years and 5 years distant progression free survival of 31% and 15%, respectively, was obtained.

The main problem with this approach is that the pooled sensitivity and specificity of choline PET/CT is higher than 85% on a per patient basis, but not on a per lesion basis (19). In fact, 67% of patients treated with SBRT only to the positive lymph nodes experienced pelvic or retroperitoneal lymph nodal relapses (26), while the pattern of recurrence seems to be prevalently distant when prophylactic irradiation of the regional lymph-nodes is concomitantly performed (20). Thus, although choline PET/CT is the best available diagnostic tool, its limitations (27), in our opinion, imply the necessity of prophylactic irradiation of the lymph-node chains adjacent to the positive lymph-nodes.

The situation is clearly different for bone oligometastasis. Due to the low vascularization, bone progression does not reflect the pattern of progression by continuity occurring at the lymph-nodal level. In addition, patients diagnosed with few bone metastases are more likely to harbour a real oligometastatic phenotype (9), and the combined sensitivity, specificity, positive- and negative- predictive value of both choline PET/CT and bone scan lead to far greater diagnostic accuracy (18); diagnostic omissions, such as for lymph-nodes are very unlikely. Thus, SBRT is more suitable for bone oligometastatic patients.

The number of lesions allowed for metastatic patients enrolled for radical treatments should probably be decreased from 5, as in the original definition, to 3 or fewer, as demonstrated by recent studies and looking at the natural history (25,28,29). A biological equivalent dose higher than 100 Gy should be provided, in the case of radical intent, to oligometastasis (1,23).

In the near future, new tracers, targeting the prostate-specific membrane antigen (PSMA), will help in the proper selection of patients for radical treatments. Its overexpression in prostate cancer tissue has improved the sensitivity of lesion detection, even of small lymph-nodes at low PSA levels (30). Furthermore, the addition of MRI has the potential to integrate the diagnostic path in case of moderate PSMA tracer accumulation (30).

The results of several ongoing prospective trials investigating the use of SBRT in oligometastatic patients are expected to provide further indications concerning therapeutic strategy. NCT01558427 is a randomised trial whose objective is to observe the delay of palliative ADT in non castration resistant prostate cancer patients with three or fewer metastases, treated with SBRT *vs*. active surveillance and ADT at progression. NCT01777802 is an observational trial for patients with three or fewer metastases, with either treated or untreated primary prostate cancer, managed with SBRT, to observe the induction of anti prostate cancer immunity. NCT01859221 and NCT02192788 are single arm phase II trials, evaluating progression free survival in oligometastatic prostate cancer patients treated with SBRT, compared to historical controls. NCT0256391 is a phase I/II non randomised trial, evaluating late radiotherapy toxicity; lastly, NCT02264379 is a prospective observational trial comparing toxicity of hypofractionated versus standard fractionation radiotherapy treatments for oligometastasis (up to five lesions).

In conclusion the studies and meta-analysis published to date have demonstrated good results obtainable with radical treatments (BED >100 Gy) in nodal or bone oligometastatic patients. We are still in the early stages of our comprehension of a continuously evolving paradigm on metastatic progression, and are not yet fully able to select patients on the basis of molecular analysis. However,

the likely differences between the metastatic evolution of lymph-nodal and bone metastasis render them two separate entities requiring different treatment strategies. Choline tracers have revealed some limits in identifying all lymph-nodal lesions, but have high accuracy in detecting bone metastasis, another reason that makes the latter more suitable for SBRT. The newly arrived 68 Ga PSMA is a promising tracer which can improve patient selection and tailor treatments. Natural history and the results of recent studies seem to converge in suggesting a modification of the definition of oligometastatic disease to up to three lesions.

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