Editorial

Benefit from local treatment of the primary tumor in patients with metastatic prostate cancer at diagnosis

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Prostate cancer is a frequently diagnosed malignant tumor in older men. The majority is treated with curative intent in a localized stage with either radiotherapy or radical prostatectomy (1). Patients with the diagnosis of metastatic prostate cancer at diagnosis have 5-year survival rates of about 30% (2). Standard first-line treatment is an androgen deprivation therapy (ADT). Initial treatment can also include additional chemotherapy (3).

The treatment of the local tumor in patients with oligometastatic tumors is discussed increasingly in the last years, including patients with prostate cancer (2,4-7). Decrease of the tumor burden, including the source of potential metastatic seeding, can well explain prolonged survival rates and even cure in rare cases. Recent developments of molecular and clinical imaging such as prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) or modern magnetic resonance imaging (MRI) techniques help to detect lymphatic and/or haematogenous metastases at an earlier point in disease progression (8).

A biological rationale can be the elimination of cytokine signaling. Abscopal effects have been reported following radiotherapy, demonstrating regression of metastases at distant sites, though only the local tumor was treated (9). As this decision is based on several individual factors in only a selected group of patients, prospective studies in larger patient groups have not been published yet.

SEER (Surveillance, Epidemiology, and End Results)-based reports and an institutional series suggested a potential survival benefit for local treatment in selected patients with metastatic prostate cancer (10-12). A recently published NCDB (National Cancer Data Base, capturing 70% of tumors diagnosed in the United States) analysis, with a total of 15501 patients diagnosed in the years 2004–2012 with metastatic prostate cancer, included baseline patient characteristics [as Gleason score, TNM stage and Charlson Comorbidity Index (CCI)] to define patients that benefit most from local treatment (13). Local treatment was defined as radical prostatectomy, brachytherapy and/or external beam radiotherapy (EBRT) to the prostate (with or without ADT) within six months of diagnosis. Two arms (local treatment *vs.* no local treatment) were defined and matched using propensity scores to minimize selection bias. Patients with local treatment were younger, had lower PSA values, less frequently poorly differentiate tumors, less frequently lymph node involvement and lower CCI scores (all $P<0.001$).

Only 1,470 patients, corresponding to 9.5%, received a local treatment (77% EBRT, 20% prostatectomy, 3% brachytherapy), with a 3-year overall survival benefit in comparison to patients without local treatment (63% *vs.* 48%; $P<0.001$). Nonlocal treatment consisted of ADT alone (69%), watchful waiting (22%) and EBRT not targeted to the prostate (9%). Local treatment with ADT was more favorable than local treatment without ADT, with 3-year overall survival of 69% *vs.* 48% ($P<0.001$). Stratification based on treatment type resulted in 3-year survival of 80% after brachytherapy, 78% after prostatectomy and 60% after EBRT ($P<0.001$).

A propensity score matched cohort (1,462 pairs) has been evaluated additionally. There was no statistically significant difference except for median PSA value, which was 19.5

vs. 16.4 ng/mL in patients treated with local treatment *vs.* nonlocal treatment (P=0.03). At 3-year, overall survival rate was 69% *vs.* 54% in favor of local treatment (P<0.001). Local treatment was an independent predictor for overall survival on multivariable analysis.

Apart from local treatment, age, Charlson comorbidity index and the known prognostic factors as PSA, Gleason score and TNM stage were independent predictors for overall survival in multivariate Cox regression analysis. The independent predictors for survival without local treatment were used to predict survival for the entire cohort and plotted against observed survival. The benefit of local treatment decreased progressively as predicted overall mortality risk increased, so that patients with a predicted 3-year mortality risk >70% did not benefit from local treatment. A risk calculator has been developed. Patients with a relatively low tumor risk without comorbidities were found to be the best candidates for local treatment.

The results were comparable with a SEER database analysis, reporting 5-year overall survival of 67% *vs.* 53% for patients after brachytherapy or radical prostatectomy *vs.* no local treatment (10). Previous reports were not able to address the treatment modality, lacked comorbidity data or were limited to older patients >65 years. Even in a localized prostate cancer, there are no data for the superiority of one local treatment over another, in particular radiotherapy in comparison to radical prostatectomy (3). Thus, the decision for a specific local treatment has to be based on individual patient criteria, as suitability for anaesthesia, or patient preferences. A lower survival rate following EBRT in comparison to brachytherapy or prostatectomy is most probably the results of a selection bias, as patients with many comorbidities or locally advanced tumors are usually selected for EBRT.

The published NCDB database analysis did not provide complete information regarding the number and site of metastatic disease, warranting investigation in future studies. Almost 50% of patients with metastatic prostate cancer were excluded from the study cohort with missing data, limiting generalizability.

In oligometastatic prostate cancer, several different options are available to eradicate metastases. Stereotactic body radiotherapy is a well tolerated and efficacious treatment for lymph node and bone lesions, slowing down biochemical and clinical progression (14). Lymph node dissection can be performed in combination with a primary radical prostatectomy or as a salvage treatment. Lymph node metastases alone, bone metastases alone or in association with lymph node, lung metastases, and liver metastases were associated with a median overall survival of 27, 19, 16, 14 and 10 months, respectively (15).

Recent developments of molecular imaging, as PSMA-PET/CT or multiparametric MRI techniques improve the initial diagnostic accuracy (16), so that small metastases can be detected earlier. These patients have been treated locally in the past, though metastases were present, in particular patients with locally advanced prostate cancer. Nevertheless, molecular imaging techniques as PSMA PET/CT or whole body MRI are not recommended for initial staging in current guidelines (3), as a benefit could not been demonstrated yet.

Furthermore, new predictive markers will probably help to detect new cancers, metastatic cancers or identify patients who will benefit from a local treatment in metastatic cancer. Liquid biopsies hold great promise for personalized medicine due to their ability to provide multiple non-invasive global snapshots of primary and metastatic tumors. Circulating tumor cells or molecules can be identified in different body fluids, as serum, plasma, urine or seminal plasma (17).

Several new systemic treatments, as docetaxel, cabazitaxel, enzalutamide, arbiraterone, radium-223 and sipuleucel-T, have been introduced in the last years in castrate-refractory prostate cancer, based on studies showing a survival benefit. These treatments will be increasingly introduced in the initial treatment of locally advanced or metastatic prostate cancer to improve outcomes. Upfront docetaxel is already applied in clinical routine in patients with a good performance status, based on the results of phase III trials (18). Several studies suggested clinical implication of neoadjuvant chemohormonal therapy for oncological outcomes (19).

In summary, currently available data in the literature and individual experience in most prostate cancer centers suggest a survival benefit of local prostate cancer treatment in oligometastatic prostate cancer in good general health. These data justify the design of larger multicenter prospective studies to provide further evidence for this treatment concept and the selection of patients. Information on toxicity, functional outcomes and quality of life needs to be addressed in the future. Prospective phase II trials (as NCT02454543 and NCT02458716, evaluating the impact of radical prostatectomy in metastatic prostate cancer) are currently recruiting patients. Phase III trials are mandatory to establish local treatment in selected patients with metastatic prostate cancer as standard treatment.

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Footnote

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