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TOPIC PAPER

Metastasectomy for visceral and skeletal oligorecurrent prostate cancer

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Abstract

Objectives Metastasis direct therapy (MDT) is a common practice in different fields of oncology. However, there is a lack of data on surgical MDT in visceral/skeletal oligometastatic prostate cancer (PCa). We aimed to assess the role of surgical excision of visceral and skeletal PCa recurrence.

Methods Seventeen PCa patients experienced metachronous visceral or skeletal oligometastatic recurrence following maximal local treatment. Oligometastatic recurrence was defined as 1–3 lesions, detected with the best imaging technique available at the time of diagnosis. All patients underwent metastasectomy and were followed for a median of 43 months. Postoperative complications were graded using the Clavien–Dindo classification of surgical complications. Kaplan–Meier plots were used to assess overall survival.

Results Fourteen patients (82%) had visceral lesions, two had bone lesions (12%), and one had an abdominal wall metastasis (6%). Four patients (24%) were under active ADT at the time of metastasectomy. PSA decreased after metastasectomy in 16 (94%) patients. Ten (77%) of the 13 ADT-naïve patients had a PSA decrease of ≥ 50%. Following metastasectomy, 16 (94.1%) patients developed metastatic recurrence of which 11 (64.7%) were again oligometastatic, amenable for repeated MDT. The median time to metastatic recurrence was 14 months (range 6.4–40). We observed 8% Clavien–Dindo grade 3–4 complications in 21 procedures.

Conclusions In this report, we analyzed the outcomes of surgical excision of visceral and skeletal PCa recurrence following primary treatment. We found that removing metastasis to the bone and viscera can be associated with long-term disease-free periods at a low rate of serious complications. These exploratory results should be confirmed in prospective studies.

Keywords Prostate cancer · Oligometastatic · Surgery · Radiotherapy · SBRT · Metastasectomy

Introduction

Metastatic prostate cancer (PCa) may follow different clinical scenarios, but the most common presentation is that of recurrent disease following primary local treatment. Clinical progression-free survival in patients who experience biochemical recurrence (BCR) after radical prostatectomy ranges between 6.6 and 10 years when routine imaging (bone scan and abdominopelvic CT scan) is used [1, 2]. Patients with BCR without evidence of metastases are commonly observed until visible lesions occur or receive androgen deprivation therapy (ADT) [3]. Many of those already have micrometastatic or oligometastatic disease (1–3 lesions) [4] not yet visible at routine imaging. However, with the emergence of new imaging modalities such as choline and

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PSMA-PET/CT, the landscape of biochemically recurrent PCa has changed. Compared to conventional imaging, these new techniques have an increased accuracy to detect recurrence at low PSA values [5–7]. As a consequence, more patients are now diagnosed with oligometastatic recurrence, creating a window of opportunity for metastasis-directed therapy (MDT) [8]. Recently, the results of a randomized phase-2 trial showed a benefit for MDT compared to surveillance in prolonging ADT-free survival in oligorecurrent patients [9]. Most patients in this trial received stereotactic body radiotherapy (SBRT) and had recurrence confined to the lymph nodes only. In another prospective phase-2 study, 93% of patients with bone metastasis (M1b) treated with SBRT showed local radiological control at 2-year follow-up [10]. As a consequence, several prospective trials on SBRT for oligometastatic PCa are ongoing (NCT01728779, NCT02192788, NCT01777802, NCT01859221) [11].

In contrast, there is a lack of data on surgical treatment of oligometastatic patients with skeletal or visceral recurrence. Therefore, the role of metastasectomy in these patients remains unclear. Several case reports have reported the feasibility of metastasectomy in PCa in highly selected patients [12–14]. The demonstration of feasibility, tolerability and improved oncological outcome of patients receiving metastasectomy is the first step before testing its hypothetical benefit in randomized controlled trials. In this study, we report the outcomes of patients treated with surgical excision of skeletal and/or visceral oligometastatic PCa in an exploratory, retrospective, bi-institutional study.

Methods

After obtaining approval of both institutional ethical review boards (internal study number: S61342), we retrospectively collected clinical data of oligometastatic PCa patients undergoing metastasectomy for oligorecurrent disease at two tertiary referral centers. Prior to metastasectomy, every patient was extensively discussed at the multidisciplinary board meeting and counseled regarding different treatment options: initiation/continuing ADT, SBRT or metastasectomy. Patients were aware of the experimental nature of the surgical approach and consented to undergo resection of all suspected metastatic lesions.

Inclusion and exclusion criteria

Inclusion criteria were the following: biopsy-proven initial diagnosis of prostate adenocarcinoma, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, at least one skeletal or visceral lesion on imaging which was deemed eligible for complete surgical resection and pathological confirmation of prostate adenocarcinoma of the excised lesions. Exclusion criteria were: prior MDT such as radiotherapy or surgery, concomitant lymph node recurrence, more than three lesions and lesions which were not resectable, prior systemic treatment for PCa other than ADT and ECOG performance status > 1.

Covariates

The following clinical variables were collected: type of primary treatment, disease characteristics at primary treatment (pTNM, pGleason, PSA), adjuvant/salvage ADT or radiotherapy treatment prior to metastasectomy, type of imaging at time of BCR, site of positive imaging (skeletal, visceral or both), ADT at time of metastasectomy, PSA before and after metastasectomy, percentage PSA decrease, postoperative complications graded using the Clavien–Dindo classification [15], time until second relapse and date of the last follow-up or death.

Statistics

Summary statistics for categorical variables were reported using proportions and frequencies. Non-normally distributed continuous variables were reported by medians and interquartile ranges (IQR) and normally distributed continuous variables by means and standard deviations (SD). Kaplan–Meier plots were used to assess overall survival. Statistics were performed using the statistical software MedCalc (statistical software version 18.9, MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

Results

Seventeen consecutive patients with skeletal and visceral oligometastatic disease (1–3 lesions) who received metastasectomy from 2007 until 2015 were included in the analysis.

Patient characteristics

Table 1 provides an overview of the patient characteristics at primary treatment and Table 2 at time of MTD. At time of MDT, the majority of the patients (88%) were asymptomatic and had excellent ECOG performance status (ECOG 0: 71%). Thirteen patients (76.5%) were ADT-naïve before MDT. Four patients were previously treated with bicalutamide or an LHRH agonist. Testosteron level at time of MDT was unknown. The metastases were detected using the most accurate imaging techniques available at the time of presentation. All included patients had a single metastasis, mostly located in the lungs (41.1%).

Table 1 Clinico-pathological characteristics at time of primary treatment

All patients ($n=17$)	
N°/median (IQR)	
Age at primary treatment	58.5 (55.5–61)
Type of primary treatment	
EBRT	1
RP	13
NA	3
PSA pre-treatment	12.4 (6.8–19)
Biopsy Gleason	
< 7	3
7	4
8–10	6
NA	4
cT stage	
< T3a	5
T3a	6
T3b–T4	2
NA	4
Adjuvant/salvage RT	
Yes	10
No	2
NA	5
Adjuvant/salvage ADT	
Yes	4
No	13
Patients treated by radical prostatectomy ($n=13$)	
pT stadium	
T2	4
T3a	4
T3b–T4	3
NA	2
pN stadium	
N0	6
N1	4
NA	3
pGleason score	
< 7	1
7	3
8–10	8
NA	1

EBRT external beam radiation therapy, *RP* radical prostatectomy, *ADT* androgen deprivation therapy, *MDT* metastasis-directed therapy, *IQR* interquartile range, *PSA* prostate-specific antigen, *NA* not available

Oncological outcome and postoperative complications of MDT

Median preoperative PSA was 4.2 ng/ml (range 1.5–8.2) with a median PSA doubling time of 7.5 months (range 2–83). PSA decreased after metastasectomy in 16 (94.1%) patients (Supplementary Fig. 1). Ten (77%) of the ADT-naïve patients had a PSA decrease ≥ 50% and PSA decrease ≥ 70% in all patients under ADT. Patients were periodically followed with PSA and imaging. Median time from MDT to first PSA rise was 2 months (range 0–13). The median time to subsequent metastatic progression was 14 months (range 6–40). Most metastatic recurrences (11/16, 69%) were oligometastatic and were again considered for MDT. Additional MDT was proposed until evidence of polymetastatic disease (> 3 lesions) at follow-up imaging (Fig. 1). Subsequent MDT was discussed at the local multidisciplinary tumor board in each participating institution. SBRT was proposed as an alternative when surgery was no longer considered an option.

PSA changes after second MDT are shown in Supplementary Fig. 2. After up to three sequential sessions of MDT, six patients (35%) were radiologically disease-free at the last follow-up. This observation is important, as it demonstrates that repeated MDT, starting with metastasectomy, can obtain complete remissions in selected patients with oligometastatic skeletal/visceral PCa. After a median follow-up of 43 months (range 38–61), three patients died of PCa (17.6%), two died of other causes (11.8%), and 12 (70.5%) were still alive. The 4-year overall survival was 66% (Supplementary Fig. 3).

We also assessed postoperative complications using the Clavien–Dindo classification of surgical complications for 21 metastasectomy procedures (Supplementary Table 1). In total, 90% of complications were Clavien–Dindo grade 0–2, supporting the safety of these procedures. Two cases had, respectively, a grade 3b (wound dehiscence) and 4a (hemorrhage from the rectum) complication.

Conclusions

Since the introduction of novel imaging techniques such as choline and PSMA-PET/CT, more patients with BCR following primary treatment are diagnosed with low-volume metastatic prostate cancer, leading to a shift in treatment paradigm toward MDT [16]. The idea of directing treatment to the oligometastatic lesions is based upon the hypothesis that the excision/irradiation of metastases could antagonize the vicious circle of metastatic cross-talk giving rise to new lesions [17]. In a recent article, Weichselbaum updated his hypothesis on oligometastatic disease which was published about 20 years earlier [18]. He reiterated the therapeutic advantages of targeting oligometastatic disease, insisting on an ablative approach (using radiotherapy with or without surgery), combined with systemic therapy (e.g., immunotherapy) in a concept of personalized medicine and integration of different approaches [19]. Surgical resection of

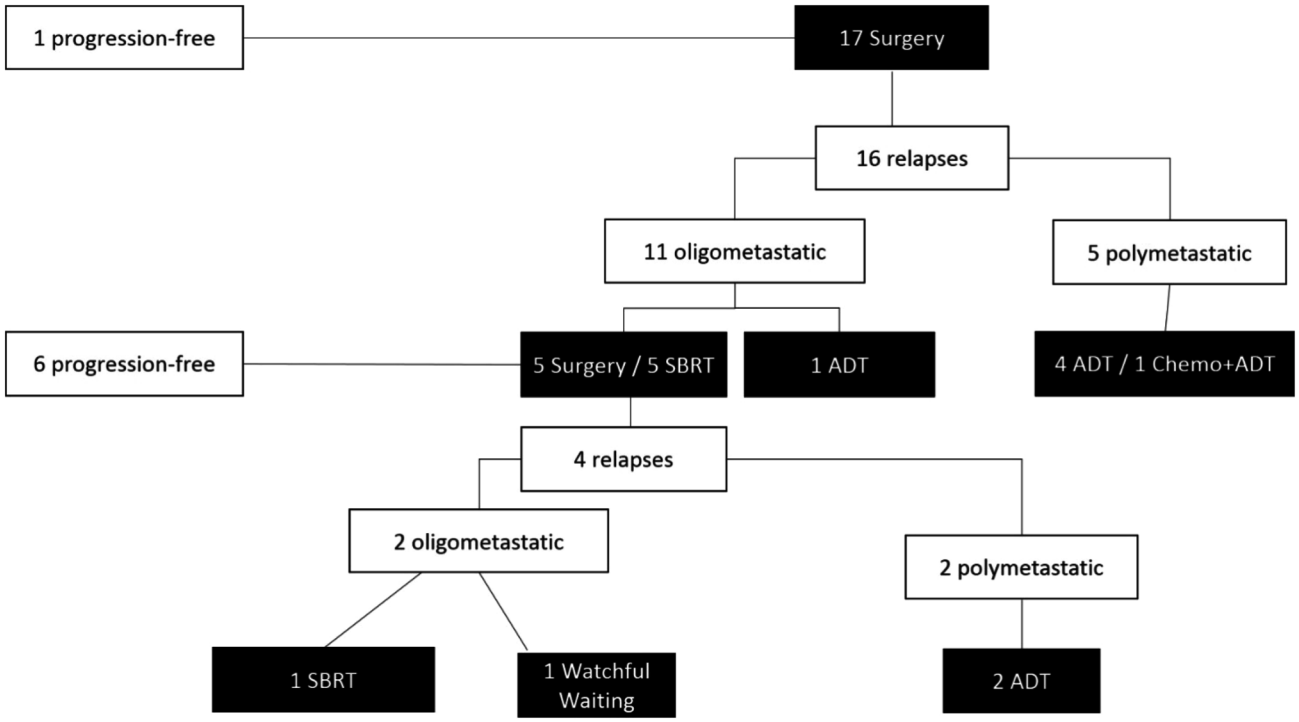
Table 2 Clinico-pathological characteristics at time of MDT

	First MDT ($n=17$)	Oligometastatic relapse after first MDT ($n=11$)
	N°/median (IQR)	
Age at MDT	65.5 (62–70.5)	67 (63–71)
PSA		
PSA pre-MDT (ng/mL)	4.2 (1.5–8.2)	1.0 (0.4–1.7)
PSA post-MDT (ng/mL)	0.5 (0.3–2.9)	0.7 (0.1–1.9)
PSA decline (%)	77.4 (58.7–90)	43.2 (− 17.7 to 71.4)
PSA-DT (months) following MDT	2 (1–3)	4 (3–6)
PSA decline (ng/mL)	2.2 (0.8–3.7)	0.1 (− 0.2 to 1.7)
PSA undetectable (≤ 0.1)	3	2
0.1 > PSA < 1	9	4
PSA ≥ 1	5	4
Imaging		
Choline-PET/CT	12	2
FDG-PET/CT	3	1
PSMA-PET/CT	1	6
CT		1
WB-MRI		1
Bone scan	1	
Timing		
Time between MDT and radiological relapse (months)	–	14 (6.5–40)
Anatomical site of recurrence		
Axial skeleton	2	
Appendicular bone		2
Abdominal wall	1	
Lung	7	3
Liver	1	
Testis	1	
Bladder	1	
Rectum	1	
Extensive local recurrence after RP and RT	1	2
Corpus spongiosum	1	
Pelvic lymph nodes		2
Retroperitoneal lymph nodes		1
Mediastinal/Hilar lymph nodes (lung)	1	1

MDT metastasis-directed therapy, *IQR* interquartile range, *PSA* prostate-specific antigen, *PSADT* PSA doubling time, *PET* positron emission tomography, *CT* computed tomography, *FDG* fluorodeoxyglucose, *PSMA* prostate-specific membrane antigen, *WB* whole body

oligometastatic disease also provides an important source of biological material which can be used for the development of biomarkers and can aid in elucidating the molecular biology of oligometastatic disease. Although data on the surgical treatment of visceral and skeletal recurrence are scarce, the therapeutic effect of SBRT in this setting is promising [20–22]. In addition, the benefit of metastasectomy in other cancer types with similar or higher proliferation index such as colorectal and renal cancer is already well known [23–25]. This study is the first attempt to elucidate the role of surgery in oligometastatic PCa patients with visceral or skeletal recurrence.

It is not possible to draw strong conclusions from our observational case series because of the absence of a comparator and the limited/retrospective nature of our study. However, several observations are noteworthy. First, 65% (11/17) patients obtained a PSA decline of ≥ 70%. Second, patients who are generally considered to be candidates for systemic therapy can obtain a complete radiological response when applying surgical MDT. Third, although



SBRT: stereotactic body radiotherapy; ADT: androgen deprivation therapy

Type of progression		After metastasectomy	After second MDT
Oligometastatic	(n°)	11	2
Polymetastatic	(n°)	5	2
Progression-free	(n°)	1	6

Fig. 1 Flow diagram showing the clinical course of patients who underwent primary or secondary metastasectomy for treatment of PCa

most patients experienced metastatic recurrence, two-third are again oligometastatic and amenable for repeated MDT. Fourth, complication rates of surgical MDT are acceptable in well-selected patients. Finally, we demonstrated convincing 4-year overall survival when applying surgical MDT in bone and visceral oligorecurrent PCa.

We report the first feasibility series for visceral and skeletal surgical MDT showing that the procedure is applicable and safe in selected subjects with oligometastatic PCa. The promising PSA response after surgical MDT, the long metastatic recurrence-free period and the oligometastatic recurrence pattern support the idea that these patients are affected by metastatic recurrence with less-aggressive biology. However, the survival impact of such approach remains a research question and should be addressed in future randomized controlled trials.

Author contributions LT and SJ helped in protocol/project development. AB, LT, MW, KD, GD, CB, AT and SJ contributed to data collection or management. AB, TL, GD and SJ analyzed the data. GD, AB, LM, WE, MA, TVdB, LT, GDM, PO, HVP, KG and SJ edited and wrote the manuscript.

Compliance with ethical standards

Conflict of interest Lorenzo Tosco: research grants from Bayer, Ipsen, Ferring, Janssen; Consulting or Advisory Role from Ipsen. Travel, Accommodation, Expenses from Astellas, Bayer and Pierre-Fabre.Steven Joniau: research grants from Bayer, Ipsen, Ferring, Janssen; Honoraria from Bayer, Astra Zeneca, Ferring, Astellas, Ipsen, Janssen. Travel, Accommodation, Expenses from Bayer, Astra Zeneca, Ferring, Astellas, Ipsen, Janssen.

Ethical standard The study (S61342) was approved by the Ethics Committee of the UZ/KU Leuven—Leuven (Belgium), on June 26, 2018. The study was conducted in compliance with the principles of the Declaration of Helsinki (2013), the principles of Good Clinical Practice

and in accordance with all applicable regulatory requirements. This manuscript involves human participants.

Informed consent For this type of study formal consent is not required.

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