Prostate International 7 (2019) 125–130

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Review Article

Role of surgery in oligometastatic prostate cancer

Pocharapong Jenjitranant [a, b], Karim A. Touijer [b, *]

[a] Division of Urology, Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 270 Rama VI, Bangkok, 10400, Thailand
[b] Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

ARTICLE INFO

Article history:
Received 24 May 2019
Accepted 14 June 2019
Available online 3 December 2019

Keywords:
Cytoreductive radical prostatectomy
Metastatic prostate cancer
Oligometastatic prostate cancer
Radical prostatectomy
Surgery in metastatic
Treatment of primary tumor

ABSTRACT

Androgen deprivation therapy as single modality therapy was the standard management for oligometastatic prostate cancer (PCa). Current paradigm shifts toward a multimodality therapy approach, targeting all sites of disease, including treatment of the primary in the form of radical prostatectomy or radiation therapy. The objective of this article was to reveiw the literature regarding the role of surgery in oligometastatic PCa. PubMed and MEDLINE electronic databases were queried for English language articles from January 1, 1980 to March 31, 2019. Keywords use included oligometastatic PCa, metastatic prostate cancer (mPCa), radical prostatectomy, and cytoreductive prostatectomy. Preclinical, prospective, and retrospective studies were included. There is no published randomized controlled trials, evaluating the role of surgery in mPCa. Preclinical and retrospective data suggest benefit of primary tumor treatment in mPCa. Current literature supports the concept of cytoreductive surgery as it can prevent late symptomatic local progression, has acceptable complications, and may prolong survival in patients with mPCa. Surgery is a feasible procedure in mPCa which may improve outcome in mPCa. However, there is no Level 1 evidence, yet that support the role of surgery in mPCa. The results from well-organized prospective, randomized controlled trials are awaited before performing radical prostatectomy for mPCa in clinical practice.

1. Introduction

Oligometastatic cancer is a term first described in 1995 by Hellman and Weichselbaum as early tumors which metastasize limited in number at an intermediate state between locally confined cancer and widespread systemic metastasis. This term is in contrast to micrometastases, which may be small in size but are large in number.[1] Oligometastatic prostate cancer (PCa) continues to be defined as a disease state which is limited in total disease burden and not rapidly spreading to other sites, usually by number of metastatic lesions clinically evident or radiographically detected. Although many literatures propose various definitions of oligometastatic PCa, most of which are generally defined as less than or equal to three or five extrapelvic metastatic sites.[2–7] Our knowledge about oligometastatic cancer has continued to mature over the past two decades[8] In the meanwhile, emerging genomic data have shown different biological pathways between widespread and limited metastatic diseases for multiple primary cancers, as well as PCa[9,10]

Conventionally, local therapies such as radiotherapy and radical prostatectomy (RP) were provided only to cure the localized disease[11] However, if we could identify patients with true oligometastatic PCas whose diseases were unlikely to disseminate further from the patients destined to develop widespread metastases, there would be the benefit of aggressive therapy such as RP in these patients.[8,12,13]

2. Incidence of de novo metastatic PCa

PCa is the most common cancer and the most common cause of cancer death in Western men.[14] The incidence rates are highest in the high-income regions of the world including North America, western and northern Europe, and Oceania.[15] In the United States, there are 3.3 million men who have been diagnosed with PCa, and there is an estimated 180,000 patients to be newly diagnosed per year.[16] The increasing incidence of PCa observed in western countries has primarily been influenced by an increased use of prostate-specific antigen (PSA) testing.[17] In the Unites States, PSA-based screening has significantly increased the incidence of overall PCa

* Corresponding author.
E-mail address: touijerk@mskcc.org (K.A. Touijer).

https://doi.org/10.1016/j.prnil.2019.10.001

from the 1990s until 2012.[18,19] The age group 55-69 years that was thought to benefit from screening of PCa had the largest increase in metastatic PCa (mPCa) incidence.[20]

However, after the 2012 United States Preventive Services Task Force (USPSTF) recommendation discouraging PSA screening, the reduction in PSA screening in United States resulted in a decline in overall PCa incidence. On the other hand, there was an increase in incidence of mPCa from 2004 through 2013.[21–23] From the US Surveillance, Epidemiology, and End Results (SEER) program, the incidence of de novo mPCa during the periods from 1980 to 2011 increased from 6.7 to 9.9 per 100,000 men.[24] Weiner et al.[25] also reported that 3% of 767,550 men with PCa in their study had de novo metastases at diagnosis.

In Australia, after the amendment of the Royal Australian College of General Practitioners Preventive Activities in General Practice guidelines influenced by the publication of USPSTF guidelines, the incidence of newly diagnosed mPCa increased from 17.7% in prerelease of USPSTF group (2009-2011) to 31.5% in postrelease USPSTF group (2013-2014), which was nearly double.[26]

The incidence of de novo mPCa from the European Randomized Study of Screening for Prostate Cancer was reported to be 0.67% and 0.86% per 1000 men in screening arm and control arm, respectively. Besides, there was an absolute reduction of metastatic disease of 3.1 per 1000 men in the screening arm, hence they concluded that the risk of developing de novo mPCa could be reduced by PSA screening.[27] There was also a decrease in de novo mPCa reported by Danish Prostate Cancer Registry (DaPCaR) from 12 to 4.4 per 100,000 men during the periods from 1995 to 2011. Early detection strategy by PSA screening might help to decrease the incidence of de novo mPCa in this population.[28,29]

3. Mortality of de novo mPCa

From Southwest Oncology Group Phase III trial, Tangen et al.[30] reported an improvement of overall survival (OS) trends in men newly diagnosed with mPCa despite an increase in incidence in 2012. They discovered that the median OS in men newly diagnosed with mPCa, was improved from 30 months at preprostatic specific era to 49 months at postprostatic specific era. They hypothesized that the improvement of survival may result from significant shift to less extensive metastatic disease overtime. Similarly, Welch et al.[31] proposed that an increased rate of less aggressive features of mPCa may be caused by an early detection strategy.

However, Helgstrand et al.[29] recently reported trends of mortality rate in men newly diagnosed with mPCa analyzed from 2 national cohorts. From the study of SEER in the US, the median OS in patients diagnosed with de novo mPCa was 24.0 months; 95% confidence interval (CI), 23.4-24.4 months. Similarly, the median OS from DaPCaR was 26.0 months; 95% CI), 25.2-26.8 months.

The 5-year overall mortality (OM) after diagnosis of denovo mPCa in SEER study was 79.4%; 95% CI 78.9-79.9%. In this cohort, 5-year OM in patients diagnosed during 1980 through 1994 was decreased and consequently increased in recent periods.[24] In DaPCaR, the 5-year OM after diagnosis of de novo mPCa was 78.5%; 95% CI, 77.4-79.5%. However, 5-year OM decreased throughout the study period.[29]

In the US cohort, 5-year PCa-specific mortality of de novo mPCa was stable in patients diagnosed during 1980-1994 and increased from 54.2% (95% CI, 52.9%-55.5%) in patients diagnosed during 1990-1994 to 61.0% (95% CI, 59.2%-62.9%) in patients diagnosed during 2005 through 2008 ($P < .0001$). In the Denmark cohort, 5-year PCa-specific mortality significantly decreased from 73.4% (95% CI, 71.2%-75.6%) to 56.8% (95% CI, 54.8%-58.8%; $P < .0001$).[29]

Berg et al.[32] also reported the improvement of survival in de novo patients with mPCa over the last 20 years in Denmark. They found that median OS was longer in men diagnosed between 2007 and 2013 (39.4 months) compared with men diagnosed in 1997 (24.2 months) significantly. In the same way, 5-year cumulative incidence of PCa specific death in men diagnosed between 2007 and 2013 was lower (47%) compared with men diagnosed in 1997 (72%). The improvement of OS may mainly be explained by both lower tumor burden at diagnosis and new treatment strategy. Buzzoni et al.[33] also reported 21% reduction in mPCa mortality in Europe with an increased incidence of PCa by PSA screening. In ESRPC, there was also a reduction in overall PCa mortality for more than 13 years attributable to PSA screening.[34]

4. Standard treatment of oligometastatic PCa

The standard treatments of mPCa remain unchanged over the past decade. The systemic treatment directed at the androgen axis is used with androgen deprivation therapy (ADT) or surgical castration with or without the use of chemotherapy in hormone-sensitive PCa patients. Any forms of ADT including bilateral orchiectomy, Luteinizing hormone-releasing hormone (LHRH) agonist or antagonist are all acceptable options. There is no Level 1 evidence for or against any specific type of ADT except for impending spinal cord compressions patients which LHRH antagonists or orchiectomy are more preferable[35] For more than 5 years, systematic reviews showed that combined androgen blockade using ADT in combination with another antiandrogen has small advantage comparing with ADT alone.[36] There is also a concept of intermittent ADT that may offer protective effect against metabolic syndrome, better bone protection, and improvement in quality of life.[37] Recently, CHAARTED (chemohormonal therapy versus androgen ablation randomized trial for extensive disease in prostate cancer), GETUG-15 (ADT plus docetaxel versus ADT alone for mPCa), and STAMPEDE (systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy) trials support the use of docetaxel as the first-line therapy in patients with mPCa. These trials showed that using docetaxel in combination with ADT may delay the onset of castrate disease and improve survival in patients with high burden metastatic diseases.[38,39]

It is often thought that RP does not improve prognosis in patients whose cancer has spread systemically beyond the prostate, and removal of prostate gland in these patients may offer only palliative care by alleviating local symptoms.[40,41] Traditionally, definite local therapy such as RP is usually performed for locally or pelvic-confined PCa[11,42–44] There is no recommendation yet for surgery or radiation on the primary tumor in current practice guidelines because of the lack of high-level evidence supporting the treatment of primary tumor in patients with mPCa.[11,35,45]

National Comprehensive Cancer Network guidelines advocate the use of ADT with or without docetaxel in mPCa, whereas radiation is only used for palliative treatment of local symptoms.[45] Similarly, the European Association of Urology guidelines recommend that surgery is an ineffective treatment for mPCa, and radiation is only used for local symptom control.[11,35]

5. Concept of primary tumor treatment in oligometastatic PCa

Oligometastatic PCa is defined as a disease state which is limited in total disease burden and not rapidly spreading to other sites.[1] Genomic data have shown different biological pathways between widespread and limited metastatic diseases in several primary cancers, as well as PCa[9,10] From the “seed and soil” theory, if the facilities of metastatic growth such as fitness of individual cancer cells are not fully developed and the quality of the site for such

growth is restricted, tumors may have metastases limited in number and location.[1,46]

There is a theory that cancer cells that are left in the primary tumor as circulating tumor cells have the ability to seed metastases to distant organs. Uncontrolled local tumor may act as a source for seeding to distant organs and self-seeding the primary tumor itself. Therefore, the longer the primary cancer remains in place, the higher is risk of new malignancies and progression of metastases.[47–49]

More recently, there is a new emerging concept about the role of RP for the treatment of oligometastatic PCa. The role of surgery in mPCa is supported by several preclinical models. Kadmon et al.,[50,51] injected rats with 3327/MAT-Lu tumor which is a prostatic cancer cell line that has the potential to cause lung metastasis in 100% of cases. They found that rats underwent surgical excision of the primary tumor plus chemotherapy had improved survival comparing with those received chemotherapy alone (42% vs. 0% at 180-day sacrifice). Cifuentes et al.,[52,53]) used PC3 cells which were derived from a bone metastasis of a human PCa patient for orthotopic injection into mouse prostate. They discovered that after resection of the prostate, the metastatic sites were smaller and less numerous comparing with the control group. These preclinical studies support the hypothesis of cytoreductive surgery in mPCa.

Although there are several ongoing randomized controlled trials (RCTs) regarding the surgical management of the primary tumor in mPCa, all reports to date are observational data or retrospective reviews. Aggressive transurethral resection of the prostate (TURP) is another form of cytoreductive surgery. Qin et al.[54] retrospectively reviewed patients with metastatic hormone-sensitive PCa underwent palliative TURP and found that this resulted in a better and more prolonged response to ADT with a trend toward improvement in disease specific and OS. TURP may provide an alternative approach for cytoreductive surgery besides RP.

There are several retrospective studies about RP in mPCa. The first study was reported by Culp et al.[55] using the SEER database. They evaluated the role of local therapy in men documented stage M1a–c (American Joint Committee on Cancer stage) PCa. A total of 8,185 patients with mPCa were identified. RP was performed in 245 patients with 67.4% 5-year OS, and 75.8% 5-year disease-specific survival. Brachytherapy was performed in 129 patients with 52.6% 5-year OS, and 61.3% 5-year disease-specific survival. The remaining 7,811 patients underwent no local therapy with only 22.5% 5-year OS, and 48.7% 5-year disease-specific survival. The results suggested that local therapies with either RP or brachytherapy were associated with improved overall and disease-specific survival. However, this study had some limitations that RP was performed in only about 3% of the population, and there might be selection bias.

Antwi and Everson[56] also analyzed patients from the same SEER database with propensity score methods for risk adjustment and found similar results. They also observed that patients underwent RP after diagnosis with mPCa was associated with 73% (Hazard ratio [HR] 0.27, 95% CI: 0.20-0.38) lower risk of all-cause mortality, and 72% (HR 0.28, 95% CI: 0.20-0.39) reduced risk of death from PCa.

Heidenreich et al.[57] reported a case–control study to compare patients with minimal metastatic disease who underwent RP along with ADT with patients with mPCa who received only ADT in control group. A total of 23 patients who underwent RP in addition to ADT were the patients who had clinically localized PCa with equal or less than 3 bone metastatic sites and no visceral disease. Whereas, the other 38 patients in the control group received only ADT. Patients in RP group had significantly better clinical progression-free survival (38.6 vs. 26.5 months, $P = 0.032$), cancer-specific survival rates (95.6% vs 84.2%, $P = 0.043$), and longer median time to castration-resistant PCa (40 vs. 29 months, $P = 0.04$), but OS was not different. There was no statistically significant difference in terms of clinical stage, Gleason score, PSA, and extent of metastases between two groups. However, there were some limitations in this study that the patients in this study were not randomized, and median follow-up time of patients in the control group was longer (47 vs. 34.5 months).

Gratzke et al.[58] evaluated patients diagnosed with mPCa from the Munich Cancer Registry. Of a total of 1,538 patients in their cohort, 74 patients underwent RP. There was 55% 5-year OS rate in RP group in comparison with 21% in patients who did not undergo RP ($P < 0.01$). However, this study had a limitation that they did not evaluate baseline characteristic and pathologic reports of the patients in their study.

Recently, Gandaglia et al.[59] reported outcomes of 11 patients with oligometastatic PCa who underwent RP in a single-institutional series. These patients had a 7-year progression-free survival and cancer-specific survival rates of 45% and 82%, respectively. Although they reported favorable long-term follow-up outcomes in patients with PCa with bone metastases, this study had several limitations. First, this study was a small retrospective review with only 11 patients. Second, patients who underwent RP had good performance status, low disease volume, and favorable PSA level, therefore significant selection bias was observed. Third, there was no control group in this study, thus the oncologic outcomes could not be determined.

Another possible advantage of RP in mPCa is that it may prevent late symptomatic local progression. Patrikidou et al.[60] found that up to 78% of patients who have de nono mPCa will suffer significant local symptoms such as pelvic pain, dysuria, hematuria, and urinary retention throughout their disease course. These patients required palliative RP, cystectomy, or pelvic exenteration to alleviate the symptoms. Therefore, initial definite locoregional treatment at earlier time point in these patients may have a role to prevent the development of late local symptoms.

Recently, there are two prospective RCTs evaluating the effect of radiotherapy in patients with newly diagnosed metastatic PCa which are HORRAD (effect on survival of ADT alone compared to ADT combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial) and STAMPEDE trials. The HORRAD trial reported outcomes of patients with primary bone metastatic PCa who received ADT combined with concurrent radiation therapy comparing with the patients who received ADT alone. There was no significant difference in OS between two groups (HR 0.9; 95% CI: 0.7-1.14) with median OS of 45 months in the radiotherapy group and 43 months in the control group. However, the median time to PSA progression in the radiotherapy group (15 months with 95% CI: 11.8-18.2) was differed significantly from the control group (12 months with 95% CI: 10.6-13.4) (HR 0.78; 95% CI: 0.63–0.97, $P = 0.02$) .[61]

STAMPEDE, a multicenter randomized controlled Phase III trial compared the outcomes of ADT plus radiotherapy to the primary tumor to ADT alone, in patients with de novo mPCa.[62] This trial showed survival benefit of radiotherapy in oligometastatic PCa. There was no significant difference in OS between two groups (HR: 0.92, 95% CI: 0.80-1.06; $P = 0.266$). However, radiotherapy could improve failure-free survival (HR: 0.76, 95% CI: 0.68–0.84; $P < 0.0001$). Moreover, metastatic burden was randomized and classified using the definition from CHAARTED trial. High metastatic burden was defined as four or more bony metastases with one or more outside the pelvis or vertebral bodies, or visceral metastases, or both; all other patients were classified to have low metastatic burden.[38] OS was improved significantly in patients with a low metastatic burden who underwent radiotherapy (HR: 0.68, 95% CI: 0.52-0.90; $P = 0.007$). In addition, failure-free survival

was also improved in men with low metastatic burden (HR: 0.59, 95% CI: 0.49-0.72; $P < 0.0001$). In contrast, radiotherapy did not improve OS (HR: 1.07, 95% CI: 0.90-1.28; $P = 0.420$) and failure-free survival (HR: 0.88, 95% CI: 0.71-1.01; $P = 0.059$) for men with high metastatic burden. By conclusion, although there was no improvement in unselected patients, radiotherapy could improve survival in men with a low metastatic burden.[62] Findings from the STAMPEDE trial support the treatment of primary tumor by radiotherapy in patients with oligometastatic mPCa and is likely to set a new standard of care.

There are several ongoing prospective RCTs evaluating the role of surgery in mPCa such as a prospective multi-institutional randomized, Phase II trial of best systemic therapy (BST) vs BST plus definitive local therapy (surgery or radiation) in patients with mPCa (NCT 01751438), the impact of RP as primary treatment in patients with PCa with limited bone metastases (g-RAMPP, NCT 02454543) which comparing patients received BST alone with BST plus RP, and testing RP in men with PCa and oligometastases to the bone (TRoMbone, ISRCTN15704862) which comparing patients with oligometastatic PCa to bone receiving RP plus standard care with standard care alone.

6. Local treatment in other metastatic cancers

Decreasing primary tumor burden in metastatic disease by radical or cytoreductive surgery has shown survival benefit in many types of malignancy apart from PCa. There are several data from other oncological entities such as colon cancer, ovarian cancer, and renal cell carcinoma which reveal survival benefit from tumor burden reduction, including primary tumor resection.

In colon cancer, Verwaal et al.[63] published an RCT which evaluated standard treatment of systemic chemotherapy alone comparing with aggressive cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy followed by systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. They found that OS in patients who underwent cytoreductive surgery followed by chemotherapy was 22.3 months which was better than 12.6 months in patients who received chemotherapy alone ($P = 0.032$). Similarly, Temple et al.[64] found that resection of the primary tumor was associated with improved survival in patients with Stage IV colon cancer.

A meta-analysis to evaluate survival outcome of maximal cytoreductive surgery in patients with advanced ovarian carcinoma was performed by Bristow et al[65] Patients who underwent more than 75% maximal cytoreductive surgery had improved OS of 33.9 months comparing with 22.7 months in patients with equal or less than 25% maximal cytoreduction ($P < 0.001$).

Mickisch et al.[66] performed an RCT to compare the treatment of radical nephrectomy plus interferon-alfa–based immunotherapy with interferon-alfa alone in pateints with metastatic renal cell carcinoma. Patients who underwent cytoreductive surgery in combination with interferon-alfa had significant better OS of 17 months in comparison with 7 months in patients who received only interferon-alpha ($P = 0.03$).

7. How should we study this concept of primary treatment in oligometastatic PCa?

Prospective randomized trials are ongoing to test the role of primary tumor resection to improve survival in mPCa. Results of ADT as first-line single modality therapy in mPCa are predictably poor. Overall outcomes of mPCa are inversely related to disease burden, patients with more advanced disease will progress sooner in comparison with patients with less advanced disease. Using ADT alone in the treatment of mPCa cannot eliminate metastatic disease because there are cancer cells at the time of diagnosis that can resist and survive in a low androgen environment[35,67] In addition, systemic therapy alone cannot eradicate the primary tumor. The maximum response from ADT was observed by 8 months. However, the prostates removed by RP after 8 months of neoadjuvant ADT were rarely tumor-free[68,69]

There are several key concepts for studying of primary treatment in patients with oligometastatic PCa. One of the most important concepts to identify feasibility of RP in patients with mPCa is whether or not the complications of aggressive local surgery are outweighed by benefits. RP in mPCa should be evaluated separately from standard RP in localized PCa because of higher risk for locally advanced disease and involvement of adjacent organs.[70] As in the case–control study performed by Heidenreich et al.[57] they reported that RP in patients with mPCA is safe and feasible with the equivalent complication rates in comparison with high-risk localized PCa series. Gandaglia et al.[59] also performed a retrospective study of RP in oligometastatic PCa and found that there were 2 patients from a total of 11 patients who suffered Grade 3 Clavien complications after 5-year follow-up period.

Another important concept is to identify appropriate candidates most likely to benefit from RP because the more tumor burden of patients, the greater is risk of complications. At this time, there is no clear consensus on the definition of oligometastatic and it is unclear who will benefit from surgery.[71] Most of the studies focused on patients with low-volume metastatic disease, low PSA after receiving ADT, and absence of visceral metastasis.[72]

To avoid equivocation over the meaning of disease-free after RP, using undetectable PSA and noncastrate testosterone level as a screening at end point is reasonable. Albeit survival is the gold standard for identifying end point in clinical trials, using detectable PSA for evaluating biochemical recurrence indicates treatment failure when the objective is disease eradication.[73]

There are several ongoing prospective RCTs evaluating the role of surgery in mPCa which will help to identify effects of RP in patients with mPCa and improve our understanding of biologic heterogeneity of mPCa.

8. Conclusions

At this time, there are several ongoing prospective RCTS regarding the role of RP in oligometastatic PCa. Data from STAMPEDE represents the first Level 1 evidence in PCa, highlighting the benefit of treating the primary. A multimodality approach combining systemic therapy with surgery and radiation therapy to all detectable sites of disease is setting new standards in the management of mPca.

Conflict of interest

There is no conflict of interest.

References

1. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13:8–10.
2. Tabata K-I, Niibe Y, Satoh T, Tsumura H, Ikeda M, Minamida S, et al. Radiotherapy for oligometastases and oligo-recurrence of bone in prostate cancer. Pulm Med 2012:541656, 2012.
3. Schick U, Jorcano S, Nouet P, Rouzaud M, Vees H, Zilli T, et al. Androgen deprivation and high-dose radiotherapy for oligometastatic prostate cancer patients with less than five regional and/or distant metastases. Acta Oncol 2013;52(8):1622–8.
4. Ost P, Jereczek-Fossa BA, As NV, Zilli T, Muacevic A, Olivier K, et al. Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: a multi-institutional analysis. Eur Urol 2016;69(1):9–12.

5. Ahmed KA, Barney B M, Davis BJ, Park S S, Kwon E D, Olivier K R. Stereotactic body radiation therapy (SBRT) in the treatment of oligometastatic prostate cancer. Front Oncol 2013;2.
6. Decaestecker K, De Meerleer G, Lambert B, Delrue L, Fonteyne V, Claeys T, et al. Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. Radiat Oncol 2014;9(1).
7. Berkovic P, De Meerleer G, Delrue L, Lambert B, Fonteyne V, Lumen N, et al. Salvage stereotactic body radiotherapy for patients with limited prostate cancer metastases: deferring androgen deprivation therapy. Clin Genitourin Cancer 2012;11(1):27–32.
8. Reyes DK, Pienta KJ. The biology and treatment of oligometastatic cancer. Oncotarget 2015;6:8491–524.
9. Lussier YA, Xing HR, Salama JK, Khodarev NN, Huang Y, Zhang Q, et al. MicroRNA expression characterizes oligometastasis(es). PLoS One 2011;6(12) e28650.
10. Wuttig D, Baier B, Fuessel S, Meinhardt M, Herr A, Hoefling C, et al. Gene signatures of pulmonary metastases of renal cell carcinoma reflect the disease-free interval and the number of metastases per patient. Int J Cancer 2009;125(2):474–82.
11. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, Van Der Kwast T, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 2014;65(1):124–37.
12. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol 2011;8(6):378–82.
13. Rubin P, Brasacchio R, Katz A. Solitary metastases: illusion versus reality. Semin Radiat Oncol 2006;16(2):120–30.
14. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics. CA Cancer J Clin 2014;64(1): 9–29, 2014.
15. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer Incidence and mortality rates. Eur Urol 2012;61(6):1079–92.
16. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics. CA Cancer J Clin 2016;66:271–89, 2016.
17. Potosky AL, Miller BA, Albertsen PC, Kramer BS. The role of increasing detection in the rising incidence of prostate cancer. J Am Med Assoc 1995;273:548–52.
18. Stamey TA, Yang N, Hay AR, McNeal JF, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317:909–16.
19. Moyer V. Screening for prostate cancer: U.S. preventive services task force recommendation statement. Ann Intern Med 2012;157:120–34.
20. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al. Early detection of prostate cancer: AUA guideline. J Urol 2013;190(2):419–26.
21. Jemal A, Fedewa SA, Ma J, Siegel R, Lin CC, Brawley O, et al. Prostate cancer incidence and psa testing patterns in relation to USPSTF screening recommendations. J Am Med Assoc 2015;314:2054–61.
22. Drazer MW, Huo D, Eggener SE. National prostate cancer screening rates after the 2012 US preventive services task force recommendation discouraging prostate-specific antigen-based screening. J Clin Oncol 2015;33:2416–23.
23. Dalela D, Sun M, Diaz M, Karabon P, Seisen T, Trinh QD, et al. Contemporary trends in the incidence of metastatic prostate cancer among US men: results from nationwide analyses. Eur Urol Focus 2017;17:30118–9.
24. Scosyrev E, Messing J, Noyes K, Veazie P, Messing E. Surveillance Epidemiology and End Results (SEER) program and population-based research in urologic oncology: an overview. Urol Oncol 2012;30(2):126–32.
25. Weiner AB, Matulewicz RS, Eggener SE, Schaeffer EM. Increasing incidence of metastatic prostate cancer in the United States (2004-2013). Prostate Cancer Prostatic Dis 2016;19(4):395–7.
26. Smith S, Wolanski P. Metastatic prostate cancer incidence in Australia after amendment to prostate-specific antigen screening guidelines. ANZ J Surg 2017: 1–5.
27. Schroder FH, Hugosson JF, Carlsson SF, Tammela TF, Maattanen LF, Auvinen AF, et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2012;62:745–52.
28. Helgstrand JT, Klemann N, Røder MA, Toft BG, Brasso K, Vainer B, et al. Danish Prostate Cancer Registry - methodology and early results from a novel national database. Clin Epidemiol 2016;8:351–60.
29. Helgstrand JT, Roder MA, Klemann N, Toft BG, Lichtensztajn DY, Brooks JD, et al. Trends in incidence and 5-year mortality in men with newly diagnosed, metastatic prostate cancer-A population-based analysis of 2 national cohorts. Cancer 2018;124(14):2931–8.
30. Tangen CM, Hussain MHA, Higano CS, Eisenberger MA, Small EJ, Wilding G, et al. Improved Overall Survival Trends of Men with Newly Diagnosed M1 Prostate Cancer: A SWOG Phase III Trial Experience (S8494, S8894 and S9346). J Urol 2012;188(4):1164–9.
31. Welch HG, Gorski DH, Albertsen PC. Trends in metastatic breast and prostate cancer - lessons in cancer dynamics. N Engl J Med 2015;373(18):1685–7.
32. Berg KD, Thomsen FB, Mikkelsen MK, Ingimarsdóttir IJ, Hansen RB, Kejs AMT, et al. Improved survival for patients with de novo metastatic prostate cancer in the last 20 years. Eur J Cancer 2017;72:20–7.
33. Buzzoni C, Auvinen A, Roobol MJ, Carlsson S, Moss SM, Puliti D, et al. Metastatic prostate cancer incidence and prostate-specific antigen testing: new insights from the european randomized study of screening for prostate cancer. Eur Urol 2015;68(5):885–90.
34. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014;384:2027–35.
35. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, Van Der Kwast T, et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014;65(2):467–79.
36. Schmitt B, Bennett C, Seidenfeld J, Samson D, Wilt TJ. Maximal androgen blockade for advanced prostate cancer. Cochrane Prostatic Dis Urol Cancers Group. 2000;(2).
37. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013;368(14):1314–25.
38. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46.
39. Vale C, Burdett S, Rydzewska L, Albiges L, Clarke N, Fisher D, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol 2016;17(2):243–56.
40. Canby-Hagino E, Swanson G, Crawford E, Basler J, Hernandez J, Thompson I. Local and systemic therapy for patients with metastatic prostate cancer: should the primary tumor be treated? Curr Urol Rep 2005;6(3):183–9.
41. Potosky AL, Harlan LC, Stanford JL, Gilliland FD, Hamilton AS, Albertsen PC, et al. Prostate cancer practice patterns and quality of life: the prostate cancer outcomes study. J Natl Cancer Inst 1999;91(20):1719–24.
42. van Den Bergh RCN, Albertsen PC, Bangma CH, Freedland SJ, Graefen M, Vickers A, et al. Timing of curative treatment for prostate cancer: a systematic review. Eur Urol 2013;64(2):204–15.
43. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012;380:2018–27.
44. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009;181:956–62.
45. Mohler JL, Armstrong AJ, Bahnson RR, D'Amico AV, Davis BJ, Eastham JA, et al. Prostate cancer, version 1.2016. J Natl Compr Cancer Netw 2016;14:19–30.
46. Pienta KJ, Robertson BA, Coffey DS, Taichman RS. The cancer diaspora: metastasis beyond the seed and soil hypothesis. Clin Cancer Res 2013;19(21): 5849–55.
47. Elizabeth C, Larry N, Joan M. Clinical implications of cancer self-seeding. Nat Rev Clin Oncol 2011;8(6):369–77.
48. Morrow M, Goldstein L. Surgery of the primary tumor in metastatic breast cancer: closing the barn door after the horse has bolted? J Clin Oncol 2006;24(18):2694–6.
49. Kim M-Y, Oskarsson T, Acharyya S, Nguyen DX, Zhang XHF, Norton L, et al. Tumor self-seeding by circulating cancer cells. Cell 2009;139(7):1315–26.
50. Kadmon D, Heston WD, Lazan DW, Fair WR. Difluoromethylornithine enhancement of putrescine uptake into the prostate: concise communication. J Nucl Med 1982;23(11):998–1002.
51. Kadmon D, Heston WDW, Fair WR. Treatment of a metastatic prostate derived tumor with surgery and chemotherapy. J Urol 1982;127(6):1238–42.
52. Cifuentes FF, Valenzuela RH, Contreras HR, Castellon EA. Development of an orthotopic model of human metastatic prostate cancer in the NOD-SCIDgamma mouse (Mus musculus) anterior prostate. Oncol Lett 2015;10:2142–8.
53. Cifuentes FF, Valenzuela RH, Contreras HR, Castellon EA. Surgical cytoreduction of the primary tumor reduces metastatic progression in a mouse model of prostate cancer. Oncol Rep 2015;34:2837–44.
54. Qin XJ, Ma CG, Ye DW, Yao XD, Zhang SL, Dai B, et al. Tumor cytoreduction results in better response to androgen ablation-a preliminary report of palliative transurethral resection of the prostate in metastatic hormone sensitive prostate cancer. Urol Oncol 2012;30:145–9.
55. Culp SH, Schellhammer PF, Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. Eur Urol 2014;65(6):1058–66.
56. Antwi S, Everson TM. Prognostic impact of definitive local therapy of the primary tumor in men with metastatic prostate cancer at diagnosis: a population-based, propensity score analysis. Cancer Epidemiol 2014;38(4):435–41.
57. Heidenreich A, Pfister D, Porres D. Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control Study. J Urol 2015;193(3):832–8.
58. Gratzke C, Engel J, Stief C. Role of radical prostatectomy in clinically non-organ-confined prostate cancer. Curr Urol Rep 2014;15(11):1–6.
59. Gandaglia G, Fossati N, Stabile A, Bandini M, Rigatti P, Montorsi F, et al. Radical prostatectomy in men with oligometastatic prostate cancer: results of a single-institution series with long-term follow-up. Eur Urol 2017;72(2):289–92.
60. Patrikidou A, Brureau L, Casenave J, Albiges L, Di Palma M, Patard J-J, et al. Locoregional symptoms in patients with de novo metastatic prostate cancer: morbidity, management, and disease outcome. Urol Oncol 2015;33(5):e9–17.
61. Boeve´ LMS, Hulshof MCCM, Vis AN, Zwinderman AH, Twisk JWR, Witjes WPJ, et al. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent Radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a

prospective randomised clinical trial: data from the HORRAD trial. Eur Urol 2019;75(3):410–8.
62. Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392(10162):2353–66.
63. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21(20):3737–43.
64. Temple LK, Hsieh L, Wong WD, Saltz L, Schrag D. Use of surgery among elderly patients with stage IV colorectal cancer. J Clin Oncol 2004;22(17):3475–84.
65. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20(5):1248–59.
66. Mickisch G, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 2001;358(9286):966–70.
67. Stevens D, Sooriakumaran P. Oligometastatic Prostate Cancer. Curr Treat Options Oncol 2016;17(62):1–8.
68. Gleave ME, Goldenberg SL, Chin JL, Warner J, Saad F, Klotz LH, et al. Randomized comparative study of 3 versus 8-month neoadjuvant hormonal therapy before radical prostatectomy: biochemical and pathological effects. J Urol 2001;166(2):500–7.
69. McKay RR, Choueiri Tk, Fau - Taplin M-E, Taplin ME. Rationale for and review of neoadjuvant therapy prior to radical prostatectomy for patients with high-risk prostate cancer. Drugs 2013;73(13):1417–30.
70. Sooriakumaran P, Karnes J, Stief C, Copsey B, Montorsi F, Hammerer P, et al. A multi-institutional analysis of perioperative outcomes in 106 men who underwent radical prostatectomy for distant metastatic prostate cancer at presentation. Eur Urol 2016;69(5):788–94.
71. Jeffrey JT, Michael AG, Ashley ER, Kenneth JP, Phuoc TT, Edward MS. Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations. Nat Rev Urol 2016;14(1):15–25.
72. Metcalfe MJ, Smaldone MC, Lin DW, Aparicio AM, Chapin BF. Role of radical prostatectomy in metastatic prostate cancer: a review. Urol Oncol 2017;35(4):125–34.
73. Scher HI. Building on prostate cancer working group 2 to change the paradigm from palliation to cure. Am Soc Clin Oncol Educ Book 2014;34. e204-212.