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Metastasis-directed therapy and prostate-targeted therapy in oligometastatic prostate cancer: a systematic review

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ABSTRACT

Introduction: This review aims to summarize the available evidence on the role of metastasis-directed therapy (MDT) and/or prostate-targeted therapy (PTT) in the setting of oligometastatic prostate cancer (PCa).

Evidence acquisition: We searched PubMed, the Web of Science, and the Cochrane Library databases. The following keywords were used: (prostate cancer OR prostate carcinoma OR prostate neoplasm OR prostate tumor OR prostate tumour) AND (oligometastatic OR oligometastasis OR PSMA) AND (surgery OR prostatectomy OR radical prostatectomy OR cytoreductive OR local treatment OR radiotherapy OR stereotactic OR stereotaxic) AND (survival OR mortality).

Evidence synthesis: After evaluating the selection criteria, 81 studies were evaluated for our endpoints. We included 22 studies for PTT of synchronous mPCa. There have been no randomised studies on cytoreductive prostatectomy (cRP). Four prospective studies showed that cRP was feasible but did not contribute to a positive effect on overall survival (OS). Regarding PTT-radiotherapy, two randomised controlled phase 3 trials showed that OS was improved in men with a low metastatic burden. Regarding MDT of metachronous lymph node recurrence, we included 29 retrospective studies. For MDT of oligometastases, we included 30 studies. One randomised phase 2 trial showed that androgen deprivation therapy-free survival improved with stereotactic body radiation therapy compared to that with surveillance; however, benefits on OS remain unclear.

Conclusions: We performed a comprehensive overview of the current literature on MDT and PTT. The feasibility of MDT and PTT is supported by several retrospective studies. Nevertheless, there remains a lack of high-quality trials to prove its survival

benefits. Results from ongoing prospective trials data are awaited.

Introduction

Oligometastatic disease was proposed in 1995 as a distinct cancer condition between locally confined and systematical metastatic disease.[1] Some studies have shown that an increasing number of metastatic lesions are associated with poor outcomes in metastatic prostate cancer (PCa).[2 3] While cigarette smoking is associated with an increased risk of nocturia in patients with benign prostatic enlargement (BPE) it does not appear to be associated with PCa aggressiveness.[4] Metabolic syndrome and smoking are associated with an increased risk of nocturia in male patients with BPE.[5] Recently, new imaging modalities such as 68-Ga-labeled prostate-specific membrane antigen (PSMA) ligands, as well as whole-body magnetic resonance imaging (MRI), have been developed and are improving the detection of low volume metastatic disease.[6-8] These advances of imaging techniques allow identification of small metastases, and help to differentiate between oligometastatic and polymetastatic diseases. However, the exact definition of oligometastasis has not been determined. Furthermore, various oligometastatic situations have been envisioned (e.g. de-novo or repeat, synchronous or metachronous). Guckenberger et al. established a system for comprehensive characterization of oligometastatic disease. They developed an oligometastatic disease classification system on the basis of a decision tree of five binary disease characterization factors.[9]

Standard strategies for patients with metastatic hormone sensitive PCa are palliative treatments, including androgen deprivation therapy (ADT) plus either docetaxel or abiraterone.[10] Nevertheless, recent studies have shown that metastasis-directed therapy (MDT) or treatment of the primary tumour are associated with improved prognosis in oligometastatic PCa patients. One of the reasons is that PCa metastases can be seeded not only from the primary tumour, but also from other metastatic sites.[11 12]

The aim of this review was to summarize the available evidence on the role of MDT and/or prostate-targeted therapy (PTT) in the setting of oligometastatic PCa. These studies were evaluated using different diagnostic methods and used different definitions of oligometastasis. To identify these differences, we reviewed the diagnostic methods and the definitions of oligometastasis in all candidate papers. In addition, we confirmed the oligometastatic disease classification recently proposed by Guckenberger et al.[9]

Methods

Search Strategy

We searched PubMed, the Web of Science, and the Cochrane Library to determine the efficacy of local and metastasis-directed therapies in patients with oligometastatic PCa until December 2019. We searched articles published in the English language only. There was no restriction regarding the publication period.

After an initial screening based on study titles and abstracts, all papers were assessed based on full texts and were excluded with reasons when inappropriate; a further check of the appropriateness of the papers based on a full-text revision was performed after data extraction. The following keywords were used in our search strategy: (prostate cancer OR prostate carcinoma OR prostate neoplasm OR prostate tumour OR prostate tumour) AND (oligometastatic OR oligometastasis OR PSMA) AND (surgery OR prostatectomy OR radical prostatectomy OR cytoreductive OR local treatment OR radiotherapy OR stereotactic OR stereotaxic) AND (survival OR mortality)

Inclusion and exclusion criteria

The initial screening was performed independently by two investigators based on the titles and abstracts to check ineligible reports. We defined study eligibility using the patient population, intervention, comparator, outcome, and study design (PICOS) approach (Supplementary Table 1). We included published articles that defined the oligometastases as less than 6 distant metastases. We excluded articles not in English, including reviews, meta-analyses, guidelines, editorials, letters, and case reports. Dosimetric, motion-management, or radiotherapy planning studies, and basic science or pre-clinical studies were also excluded. Potentially relevant reports were subjected to a full-paper review, and the relevance of the reports was confirmed after the data

extraction process. Discrepancies were resolved by consensus or recourse to the senior author.

Data extraction

The information was extracted from the included articles by two investigators independently: author's name, publication year, period of registration, number of patients, status of oligometastasis, method of diagnosis, definition of oligometastatic, prostate-specific antigen (PSA), the rate of Gleason score >7, treatment, follow-up duration, oncological outcomes, and toxicity.

Results

Literature search

Overall, 2,390 publications were identified in the initial search (PubMed, 245; Scopus, 1853; Web of Science, 279) and 13 articles suggested by authors. Among these, 326 articles were excluded after screening duplicates, non-relevant articles according to inclusion criteria, books, reviews, editorial comment, case reports, abstracts only, and non-English articles. A full-text review was performed for 117 potentially relevant articles. After evaluating the selection criteria, we identified 81 articles. The selection process and list are shown in Fig. 1.

Study categorisation

Eighty-two cohorts were evaluated for endpoints in the 81 included studies. This study categorised cohorts into metachronous and synchronous cases depending on the timing of metastasis and into PTT or MDT depending on treatment modality. We included 22 studies for PTT of synchronous metastatic PCa (Supplementary Table 2). For MDT to metachronous lymph node (LN) recurrence after primary treatment with curative intent, we included 29 studies (Supplementary Table 3). For MDT to metachronous and/or synchronous oligometastases, we included 30 studies (Supplementary Table 4).

1. Definition of oligometastatic disease

There is no consensus on the definition of oligometastatic disease. Indeed, the literature provides a range of definitions based on the number of prostate metastases ($\leqq 3$ to $\leqq 5$), with variable sites (e.g. bone, LN, other organ) and based on various diagnostic imaging modalities. Conventionally, computed tomography (CT) and ^{99}m-technetium-methylene diphosphonate (^{99}mTc-MDP) are used to diagnose metastasis of PCa. The European Association of Urology recommends the use of these conventional imaging

modalities.[10] However, such imaging modalities are limited by poor sensitivity, particularly in the oligometastatic setting and by low PSA levels. Albisinni et al. reported a prospective study that PSAM PET/CT changed treatment strategy in 76% of patients compared to conventional staging.[13] This suggests that imaging modalities can significantly affect the oncological outcome of patients with oligometastatic PCa.

We summarized the distributions of "imaging modalities for detecting metastases" in Figure 2. In the category of PTT, 17 studies (77%) used conventional imaging to detect oligometastatic disease. Conversely, in the MDT to LN category, 28 studies (97%) used novel targeting imaging to detect oligometastatic disease. Similarly, in the MDT to oligometastases category, 25 studies (83%) used novel targeting imaging to detect oligometastatic disease. Regarding to the definition of oligometastatic disease, the most commonly used definition was a condition with three or less bone metastases (six studies (27%) in the PTT category, and 16 studies (53%) in the MDT to oligometastases category).

2. Role of prostate-targeted therapy in oligometastatic disease. (Table 1) [14-35]

We included 22 studies for PTT of synchronous mPCa. Using the SEER-Medicare database, Satkunasivam et al. reported a lower overall mortality risk of 57% (p=0.01) in patients who underwent RP, and of 55% (p<0.001) in patients who underwent intensity-modulated radiation therapy (IMRT) when compared with nonlocal treatment.[24] Similarly, using the National Cancer Data Base (NCDB), Löppenberg et al. reported that 3-y overall mortality-free survival was higher in the local treatment group versus the nonlocal treatment group (69% vs 54%; p<0.001).[25] These findings of retrospective analysis of several large databases suggest the efficacy of local treatment for metastatic PCa.

2.1 Cytoreductive radical prostatectomy (cRP).

There were 11 reports (robot-assisted laparoscopic radical prostatectomy (RALP) 1 report [18], RP 10 reports[14-17, 19-23], RALP or RP 1 report [27]). Seven studies were retrospective[18-23, 27] and four studies were prospective.[14-17]

Many retrospective studies revealed a benefit of cRP in patients with metastatic PCa. Kinpper et al. retrospectively investigated 78 cRP patients with low metastatic burden (LMB) (<4 bone metastases) and compared the results of STAMPEDE arm H with LMB who received radiotherapy (RT). At 3 years, OS was 91%, metastatic progression-free survival (MPFS) was 63%, and CSS was 92%, while 81%, 67%, and 86%, respectively, were reported in the RT subgroup with LMB in the STAMPEDE arm H. The authors concluded that no major disadvantage in OS and CSS may be expected when comparing the cRP cohort with the results of STAMPEDE arm H.[20] Jang et al. reviewed the records of 79 patients with oligometastatic PCa treated with RALP or ADT and showed that RALP in the setting of oligometastatic PCa improved oncological outcomes in terms of progression-free survival (PFS) and CSS.[18] Similar results have been reported by several authors.[19, 21-23] Nevertheless, we should consider potential selection bias in these retrospective studies.

There were four prospective studies that had lower selection bias. Steuber et al. concluded that there was not a significant benefit of cRP on survival; however, the rate of locoregional complications was lower.[17] Similarly, Simforoosh et al. showed that cRP did not improve cancer specific survival in patients with skeletal metastatic PCa in the short term, but offered better local control, improved biochemical relapse-free survival.[16] Heidenreich et al. showed that cRP was feasible in well-selected men with metastatic PCa who respond well to neoadjuvant ADT. [15] These prospective studies

have revealed that cRP was feasible but did not contribute to the positive effect on OS in limited patient samples. In this review, Clavien-Dindo G3 or higher adverse events occurred in 29 of the 193 patients.[14-16, 18, 20, 21]

In summary, retrospective studies showed many positive results, but prospective studies did not demonstrate any contribution to OS. Adverse events were within acceptable limits and contributed to the reduction of local symptoms, and local controls were effective. We need to wait for the results of future prospective trials. Several prospective studies are ongoing (e.g. TRoMbone trial [Testing Radical prostatectomy in men with PCa and oligoMetastases to the bone][36], the g-RAMPP trial [NCT02454543]; A Prospective, Multi-Institutional, Randomized, Phase II Trial of Best Systemic Therapy or Best Systemic Therapy (BST) Plus Definitive Treatment (Radiation or Surgery) of the Primary Tumor in Metastatic (M1) Prostate Cancer (NCT01751438); Randomized Feasibility Trial of Prostate Radiotherapy vs Prostatectomy in Men With Hormone Sensitive Oligometastatic Prostate Cancer (NCT03301701); An Open-label、Randomized Prospective Phase II Trial of ADT or ADT Plus Definitive Treatment (Radiation or Surgery) of the Primary Tumor in Oligometastatic Prostate Cancer (NCT02742675); and Local Treatment With Radical Prostatectomy (RP) for Newly-diagnosed Metastatic Prostate Cancer [mPCa] [NCT02138721] [12]), and they will provide valuable outcome results for men with newly diagnosed oligometastatic PCa who have received cRP. At this time, cRP should be performed only within clinical trials.

2.2 Prostate-targeted RT (PTT-RT)

There are two prospective randomised studies assessing the prognostic comparison between RT+ADT and ADT only. The HORRAD trial was a multicentre

randomised-controlled-trial that studied the efficacy of external beam radiation therapy (EBRT) to the prostate in addition to standard ADT in patients with mPCa, with OS as the primary outcome. The trial revealed that no significant difference in OS. Median OS was 45 months in the RT group and 43 months in the control group (p = 0.4). The trial suggested that additional radiotherapy did not improve OS. However, subgroup analysis of patients with fewer than five bone lesions showed improvements in survival when RT was added to ADT. The author noted as limitations of this study the low irradiation dose (only 70 Gy) and the lack of information regarding visceral metastases.[31]

The STAMPEDE trial was a randomizsd controlled phase 3 trial to compare the standard of care for metastatic PCa, with and without radiotherapy. The definition of metastatic burden was similar to the one used in the CHAARTED trial: high metastatic burden was defined as four or more bone metastases with one or more outside the vertebral bodies, or pelvis or visceral metastases or both; all others were considered to have a low metastatic burden. The trial suggested that the addition of radiotherapy to prostate did not improve OS (HR 0.92, 95% CI 0.80–1.06, p = 0.2266) for unselected patients with newly diagnosed metastatic PCa. However, similarly to the HORRAD trial, subgroup analysis showed that OS did improve in men with a low metastatic burden (HR 0.68, 95% CI 0.52–0.90; p = 0.007; 3-year survival 73% in controls vs 81% of patients with radiotherapy) Regarding adverse events, patients in the radiotherapy group reported a lower incidence of grade 3 and 4 Radiation Therapy Oncology Group (RTOG) acute (5%) and late (4%) effects. The author suggested that prostate radiotherapy should be a standard treatment option for men with a low metastatic burden.[32]

In summary, two prospective randomised phase 3 trials suggested that PTT-RT may be

beneficial in patients with low metastatic burden. Adverse effects were modest. Recently, accumulating evidence has indicated that fractionated radiotherapy can result in distant non-irradiated (abscopal) tumour regression.[37] This abscopal effect may be one of the potential reasons why PTT-RT is beneficial in patients with the metastatic burden.

However, it should be noted that these results are subgroup findings and that the definitions of low metastatic burden in these trials are based on conventional imaging using CT and bone scan results.

3. Role of metastasis-directed therapy (MDT)

3.1 Lymph node metastasis-directed therapy (Table 2) [38-66]

3.1.1 Conventional RT

All reports were retrospective studies. Two of the three reports used new imaging modalities to detect LN metastasis. Regarding toxicity, no grade 3 toxicity was observed. Using the Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI) platform, Bryant et al. investigated 648 patients with clinically node-positive PCa treated with ADT (n = 450) or ADT plus conventional RT (ADT-RT) (n = 198). The author reported that addition of RT to ADT was associated with substantial improvements in both PCa-specific mortality (PCSM) and all-cause mortality (ACM). Furthermore, ADT-RT was associated with a significant improvement in PCSM and ACM among patients with a pre-treatment PSA level less than the median of 26 ng/mL but not greater than the median.[38]

Other reports were from a small number of single centres. Rischke et al. evaluated 25 patients with PSA recurrence and imaging positive for LN metastases or additional local recurrence in the prostate fossa after RP using choline-PET/CT, CT and DCE-MRI (DCE-MRI). The authors concluded that patients with only one or two PET-positive LN

treated by RT achieved prolonged complete biochemical remission.[39]

3.1.2 Stereotactic body radiation therapy (SBRT)/Elective nodal radiotherapy (ENRT)

All reports on SBRT/ENRT have been retrospective studies. Among them, Nicosia et al. reported results of a relatively large number of cases treated with SBRT using multi-institutional analysis. According to their study, 109 PCa patients with LN metastasis were treated with SBRT. Local control rates at 1 and 2 years were 93.1% and 86.6%, respectively. No grade 2 or higher acute or late toxicity occurred. The author concluded that SBRT is an effective and well-tolerated treatment option for management of LN metastases from PCa.[45] Recently, the scientific community has debated focal irradiation versus elective treatment of the LN chain. De Bleser et al. compared outcome and toxicity between SBRT defined as a minimum of 5 Gy per fraction to each lesion with a maximum of ten fractions and ENRT defined as minimum dose of 45 Gy in up to 25 fractions to the elective nodes. Local progression was observed in 50 patients following SBRT and in nine patients following ENRT ($p<0.001$). The 3-y metastasis-free survival was 68% for SBRT and 77% for ENRT ($p = 0.01$). Early and late toxicities following ENRT were significantly higher than those following SBRT ($p=0.002$ and $p<0.001$, respectively). However, most side-effects with ENRT were limited to grade 2. The author concluded that nodal relapse was less frequent following ENRT than following SBRT, and thus ENRT might be the preferred treatment option.[51]

3.1.3 Salvage lymph node dissection (SLND)

There were 14 reports on (SLND (open): 8 reports [52-58, 62], SLND (robot-assisted): 2 reports[60, 61], SLND (open or robot): 1 report[59], Radioguided surgery: 3 reports[63-65]). All reports were retrospective studies. At least one of 11C-choline, 68Ga-PSMA or

18F-choline was used to detect LN metastasis. Regarding the diagnostic image, Herlemann et al. reported that patients with LN metastases diagnosed on ^{68}Ga-PSMA PET/CT showed a higher rate of complete biochemical response compared to ^{18}F-choline PET/CT (45.7 vs 21.7%, p = 0.040).[54]

Regarding to oncological outcomes, SLND can achieve PSA response rates in 41.3-79.5% of patients, with 3-y bPFS rates of 6.2-27.3%. Even if a PSA response could be achieved, there are many patients who experience biochemical recurrence. Siriwardana et al. suggests that ^{68}Ga-PSMA imaging underestimates micro-metastatic disease, therefore SLND rarely cures and recommended strict patient selection and clinical trials.[61]

Adverse events of SLND have been reported to be more frequent than normal LND.[62] In this review, 49 of 626 patients experienced Clavien-Dindo grade 3 or higher adverse events, which seemed to have more serious adverse events than other treatments. The most frequently reported complications in literature were lymphocele, fever, and prolonged ileus. However, Devos et al. reported that there were significantly fewer adverse events of robot-assisted SLND than those of the open SLND group.[59]

In summary, the evidence of MDT to LN metastases is inadequate, because most data derived from retrospective and single-centre studies. Large prospective trials with strict patient selection are required.

3.2 DMT to oligometastases. (Table 3) [67-96]

3.2.1 Conventional RT

There were four reports identified.[67-70] All reports were retrospective single-centre studies. Three of the four reports used new image modality to detect metastasis. Wu et al. reported the efficacy and toxicity of radiotherapy combined with androgen

deprivation (ADT) for bone oligometastases after primary curative RT for PCa. The 3-y OS rates were 69% and a total of 15 patients (83.3%) achieved pain relief. No grade 3 toxicity was observed.[70]

3.2.2 SBRT/ SABR/ Image-guided RT

There were 22 reports (23 cohorts).[73-94] Many retrospective studies suggest that MDT for oligometastatic PCa improves PFS.[81-91, 93, 94] Recently, nine prospective studies have been published [73-80, 92], one of which was a randomized trial. [80]

Ost et al. reported a randomized trial comparing surveillance versus MDT in a sample of 62 PCa patients who had a biochemical recurrence after primary PCa treatment with curative intent, three or fewer extracranial metastatic lesions on choline-PET/CT. With a median follow-up of 3 years, the median ADT-free survival was 13 months for surveillance group versus 21 months for the MDT group. In terms of PFS, the median time until progression was 6 months for the surveillance group, as compared with 10 months for the MDT group ($p = 0.03$). No grade 2 to 5 toxicity was observed. The authors concluded that MDT for patients with oligorecurrent PCa was safe and improves ADT-free survival when compared with surveillance and recommended testing MDT in larger phase III studies.[80] These results may be potentially advantageous in frail people in which the introduction of ADT (and particularly modern hormonal agents) could be a concern. Similar results were reported in other prospective trials, with G3 and higher toxicity being extremely rare. Pasqualetti et al. reported the prospective observational study to assess the role of ImanGuided Stereotactic Radiotherapy (IG-SBRT). Estimated 12 and 24 months local control rations were 98.7% and 97.4%, respectively. Except for one case, toxicity greater than G2 was not recorded. The author concluded IG-SBRT was safe and can be considered as a valid therapy in

patients with oligometastatic PCa.[92]

Regarding to imaging modality, Pasqualetti et al. reported a prospective study aiming to validate the role of [^{18}F]-fluoro-methyl choline ([^{18}F]-FMCH) PET/CT in the selection of PCa patients suitable for SBRT. Forty-six patients with biochemical recurrence limited up to three lesions revealed by [^{18}F]-FMCH PET/CT were enrolled and treated with SBRT on all active lesions. With median follow-up of 28.9 months, the median systematic therapy-free survival was 39.1 months. The authors concluded that [^{18}F]-FMCH PET/CT can identify oligometastatic PCa patients suitable for SBRT.[77]

In summary, these results indicate that the MDT for oligometastatic PCa patients may play a decisive role for survival and quality of life. However, there are several important limitations, such as small sample size and limited duration of follow-up. Long-term follow-up results from on-going prospective randomized trials are awaited (e.g. STOMP [80]/ORIOLE [97]).

Limitations

In this paper, we focused on a comprehensive overview on oligometastatic PCa. All current treatment outcomes were comprehensively investigated, including many single-arm retrospective studies without a control arm. Therefore, we followed the general principles of a systematic review recommended by PRISMA, but did not decide the “comparison” part including a “PICOS” framework. Second, this review included many retrospective studies, which increases selection bias. It is also possible that negative results were not published.

Conclusion

We report a comprehensive overview of the current literature regarding MDT and PTT. The feasibility of MDT and local treatment targeted to the prostate in oligometastatic PCa is supported by several retrospective case studies. Two randomized phase 3 trials suggest that PTT-RT may be beneficial in patients with low metastatic burden. One randomised phase 2 trial suggested that MDT might be beneficial of ADT-free survival but benefits of OS are unclear yet. Regarding cRP and SLND, there remains a lack of high-quality trials to prove its survival benefits. Results from on-going prospective trials data are highly awaited.

Disclosure

The authors have no conflicts of interest in this work.

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Author Contributions

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Figure legends

Figure 1

Flow chart for article selection process

Figure 2

(A) The proportions of imaging modalities for detecting metastases in the category of PTT, MDT (LN) and MDT (OM).

(B) The proportions of the definitions of oligometastases in the category of PTT, MDT (LN) and MDT (OM).

Abbreviation: PTT: prostate-targeted therapy, MDT: metastasis-directed therapy, LN: lymph node, OM: oligometastasis, NR: not reported

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Figure 1

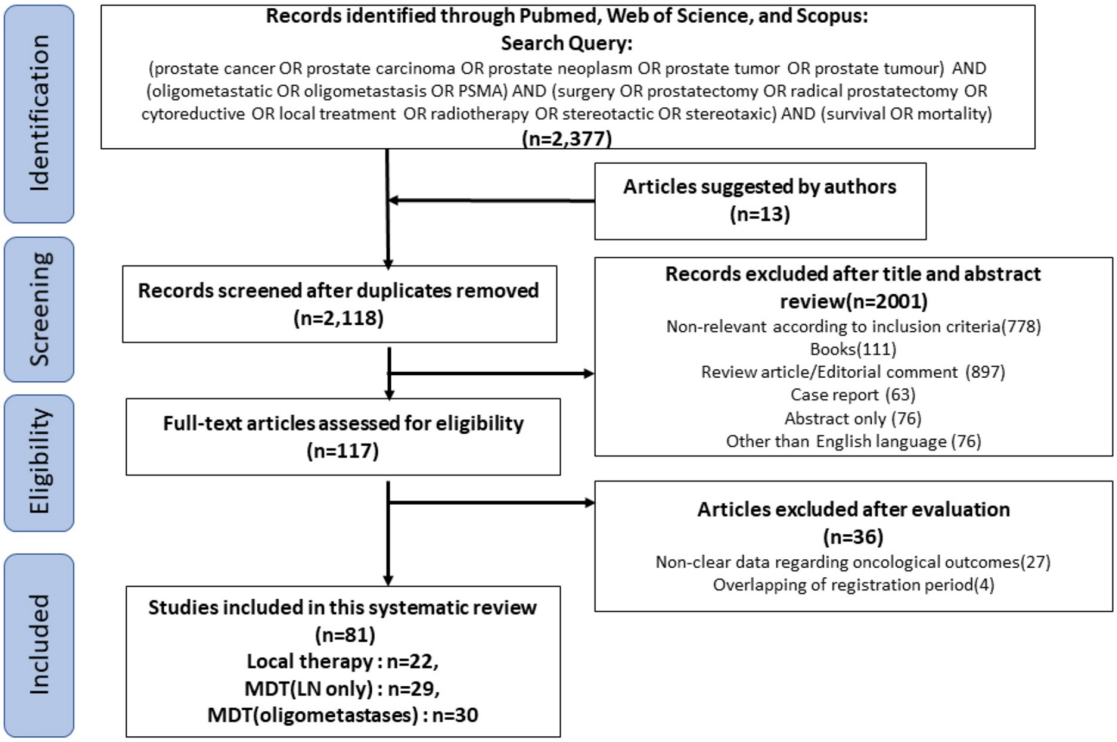
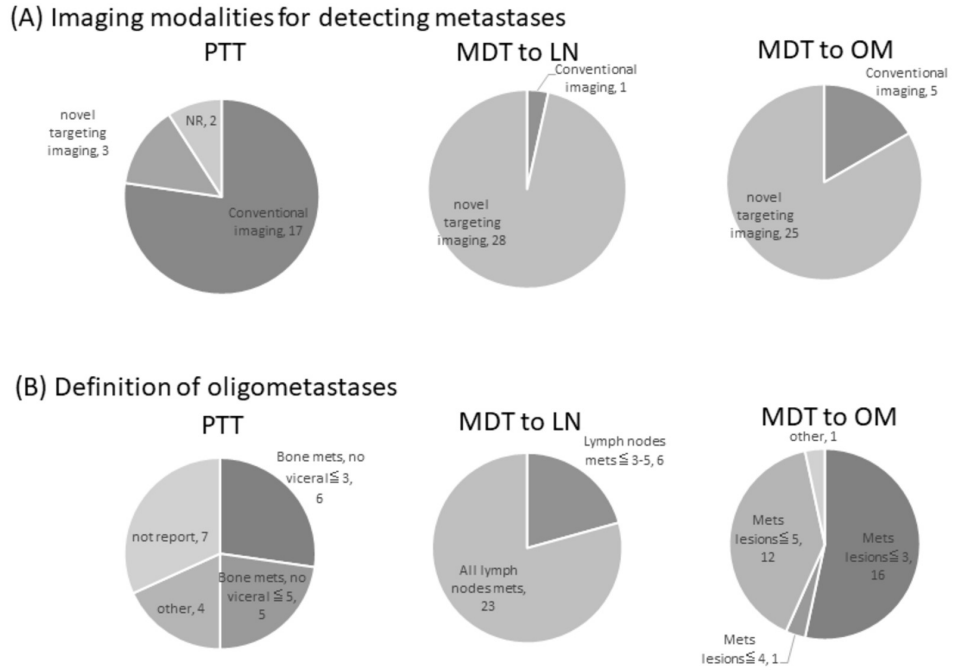


Figure 2



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