Management of Node Only Recurrence after Primary Local Treatment for Prostate Cancer: A Systematic Review of the Literature

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Purpose: We analyzed all available studies assessing the management of node only recurrence after primary local treatment of prostate cancer.

Materials and Methods: We systematically reviewed the literature in January 2015 using the PubMed®, Web of Sciences and Embase® databases according to PRISMA guidelines. Studies exclusively reporting visceral or bone metastatic disease were excluded from analysis. Eight radiotherapy and 12 salvage lymph node dissection series were included in our qualitative study.

Results: All 248 radiotherapy and 480 salvage lymph node dissection studies were single arm case series including a total of 728 patients. Choline positron emission tomography/computerized tomography was the reference imaging technique for nodal recurrence detection. Globally 50% of patients remained disease-free after short-term followup. Nevertheless, approximately two-thirds of patients received adjuvant hormone therapy, leading an overestimation of prostate specific antigen-free survival rates obtained after salvage treatment. Combining radiotherapy with salvage lymph node dissection may improve oncologic control in the treated region without improving the outfield relapse risk or the prostate specific antigen response. Great heterogeneity among series in adjuvant treatments, endpoints, progression definitions and study populations made it difficult to assess the precise impact of salvage treatment on the prostate specific antigen response and compare outcomes between radiotherapy and salvage lymph node dissection series. Toxicity after radiotherapy or salvage lymph node dissection was acceptable without frequent high grade complications. The benefit of early hormone therapy as the only salvage treatment remains unknown.

Conclusions: Although a high level of evidence is currently missing to draw any strong conclusion, published clinical series show that in select patients salvage treatment directed to nodal recurrence could lead to good oncologic outcomes. Although the optimal timing of androgen deprivation therapy in this setting is still unknown, such an approach could delay time to systemic treatment with an acceptable safety profile. Future prospective trials are awaited to better clarify this potential impact on well-defined endpoints.

Abbreviations and Acronyms

ADT = androgen deprivation therapy

CT = computerized tomography

PCa = prostate cancer

PET = positron emission tomography

RT = radiotherapy

sLND = salvage lymph node dissection

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THE role of treatment of PCa local failure is widely accepted and recommended in current clinical practice, given that it leads to a decrease in the risk of progression. However, no strong evidence supports the oncologic impact of salvage treatment in the presence of nonlocal recurrent disease.[1] Traditionally lymph node involvement has been managed only by ADT, which was considered the optimal treatment option in this setting. While such oligorecurrences should be labeled systemic, ablative treatment could delay the subsequent risk of progression and even cure limited regional nodal recurrences.

Local therapy of oligometastatic recurrence is a novel approach to PCa with a rapidly evolving literature. Thus, recent published series of sLND and salvage RT (alone or combined with salvage local treatment) have shown good outcomes associated with acceptable toxicity.[2–4] Nevertheless, to our knowledge no comparative or randomized, controlled trial has yet been published and recent new studies have been published.[3,5] For this reason it is still unknown whether such good oncologic outcomes after sLND or RT are due to favorable biological disease profile or to selective treatment of nodal metastases.

The aim of this article was to analyze all available studies assessing the impact of elective nodal recurrence treatment through a systematic review process to evaluate the oncologic outcomes and toxicities of such salvage therapies.

MATERIALS AND METHODS

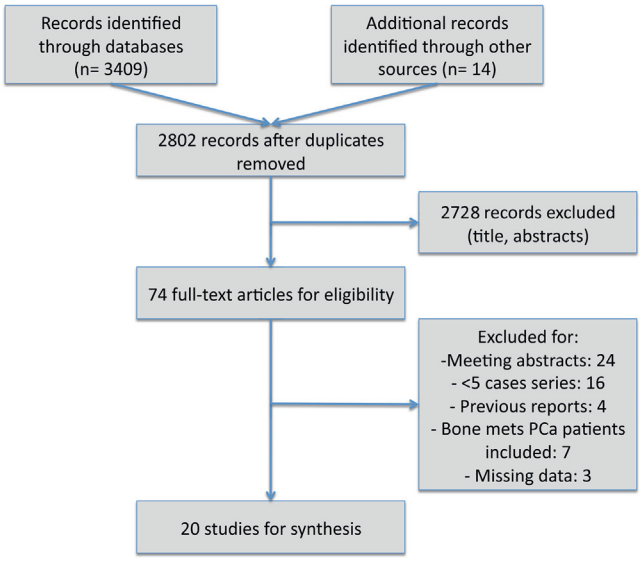
We reviewed the literature in January 2015 using the PubMed, Web of Sciences and Embase databases according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines. Search results were restricted to English language without a year limit. Key words were arranged in variable combinations. Additional references were identified from the reference list of each article. Given the low level of evidence of the studies, no exclusion regarding the evidence level was performed. To minimize publication and reporting bias case series that comprised fewer than 5 cases were excluded from analysis. Two of us (GP and VF) independently selected studies. Discrepancies between the 2 investigators were resolved via consensus. The figure shows the study selection process as a PRISMA diagram. All studies were single arm case series.[2,4,6–22]

RESULTS

Patient Screening for Nodal Recurrence

In all studies selected for our review the diagnosis of nodal recurrence was also achieved by choline PET/CT. In some patients recurrent PCa was confirmed by node biopsy before salvage treatment. The detection performance of choline PET/CT depends on the PSA cutoff and on PSA kinetics at the time of imaging. Regarding the detection of nodal recurrence after surgery the sensitivity and specificity reported in the literature ranged from 40% to 65% and from 90% to 100%, respectively.[23] Accuracy of 82% was suggested by Tilki et al with negative and positive predictive values of approximately 83% and 75%, respectively.[22] No ideal PSA cutoff has been demonstrated. The study by Tilki et al showed that the positive predictive value of PET/CT strongly depended on the PSA level, including 65% at PSA less than 2 ng/ml vs 77% at PSA greater than 2 ng/ml.[22] A recent study in 605 patients with early PSA failure after radical prostatectomy who underwent choline PET/CT suggested that PSA 1.05 ng/ml and a PSA doubling time of 5.95 months were the optimal cutoff values to predict positive imaging findings.[24] When PET/CT was followed by sLND in cases of nodal recurrence, all studies have confirmed the role of this imaging in the assessment of early recurrence upon patient analysis. However, virtually all showed that it may underestimate the real extent of nodal invasion, thus, missing further micrometastatic disease.

To date EAU (European Association of Urology) guidelines recommend choline PET/CT to detect nodal recurrences after local treatment.[1] Future



mets, metastasis