Acronyms

PCa=Prostate Cancer
LAD=Lymph node dissection
pN+ / pN1= pathologically node positive disease
RP=radical prostatectomy
cN0M0=negative conventional imaging at staging
aRT=adjuvant radiotherapy
sRT=salvage radiotherapy
Obs=observation
BCR=Biochemical recurrence
MTS=Metastasis
CSS=Cancer Specific Survival
OS=Overall Survival
ADT=Androgen Deprivation Therapy
aADT=Adjuvant Androgen Deprivation Therapy

Abstract

Introduction
More than 10% of PCa patients with negative conventional imaging (cN0M0) can be diagnosed with lymph nodes metastases when undergoing RP and LAD. Results of the sole randomized controlled trial performed in this setting date from the pre-PSA era. More recent retrospective series challenged the trial results showing not all patients with pN+ PCa should be managed in the same way. Currently optimal management of these patients remains not well defined.

Aims
Our aims were to:

i) identify research and clinical gaps including the optimal management strategies and more contemporary prognostic factors through a systematic literature search;
ii) verify the current trends in pN+ management in the urological community;
iii) a) evaluate the outcomes of Obs±sRT and b) compare Obs ± early versus aRT in the management of pN+ PCa;
iv) evaluate the role of new PET-scans as prognostic factors;
v) preliminarily evaluate novel technologies for intraoperative nodal status PCa characterization.

Methods

i) First, we performed two systematic reviews complying to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) Guidelines. The first review included retrospective and prospective single or multiple-institutions cohort studies and RCTs. The second review included registry-based studies to validate results of the first review.
ii) Second, after an expert validation, we built a 31-item survey which was distributed to members of ten urological societies and shared also using social media
iii) Third, based on i) and ii) results we created a multi-institutional database of >1,100 patients with cN0M0 PCa at conventional imaging which was subsequently found pN+ RP and LAD between 2000 and 2021 at one of 18 participating tertiary referral centers. Kaplan-Meier curves, uni- and multivariable analysis also including Cox proportional hazards models were used.
iv) Fourth, from the same database (iii), we retrospectively identified cN0M0 patients at conventional imaging (CT and/or MRI, and bone scan) who also received a pre-operative PET scan (PSMA and/or Choline). Cox proportional hazards models were used for multivariate analysis.
v) Fifth, we assessed the use of XEOS, an intraoperative specimen imager, in three men who underwent robotic RP and LAD after an injection of 68Ga-PSMA-11. In the operating theatre and after complete excision, specimens were analyzed with the imager.

Results

i) Non-registry and registry-based searches for systematic reviews were performed on 2020 and 2021 both using Medline, Embase, and other databases.
In the non-registry based review a total of 5063 articles were screened, and 26 studies including 12 537 men were finally selected. Ten-year BCR-free, clinical recurrence-free, CSS, and OS rates ranged from 28% to 56%, 70% to 92%, 72% to 98%, and 60% to 87.6%, respectively. Initial Obs followed by salvage therapies at the time of recurrence represented a safe option in selected patients with a low disease burden. The use of aRT with or without androgen deprivation (ADT) might improve survival in men with locally advanced PCa and a higher number of positive nodes. Pathological Gleason score, number of positive nodes, pathological stage, and surgical margins were key to risk stratification and selection of the optimal postoperative therapy.
In the registry based review 13 studies were included. At a median follow-up ranging 48-134months, Cancer-related death was 5% and overall-mortality 16.6%. aADT and aRT alone had no CSS or OS advantages over Obs only and over not performing aRT, respectively. aADT plus aRT yielded a survival benefit compared to Obs and aADT. Age, Gleason, Charlson score, positive surgical margins, pathological stage, and positive nodes number, but not prostate specific antigen, were most relevant prognostic factors.

ii) The survey received 253 replies. The majority believed pN+ is a multifaceted category (78.9%), stated gold standard management not being ADT (80.8%) but rather RT±ADT (52.3%) and considered early sRT±ADT an option vs. aRT±ADT (72.4%). BCR would be followed by the use of a PSMA-PET for 71% and 77% stated pN+ management being still unclear. Having PSMA-PET available had a lower and higher likelihood of considering aRT±ADT as standard and of considering early sRT versus aRT respectively on multivariate analysis ($p<.05$).

iii) The majority of patients had high risk PCa and median number of positive nodes was 1.
a) In patients undergoing Obs, at a median follow-up of 41 months (IQR 18-67), 91 patients (19.6%) experienced PSA persistence. 5-year BCR-free survival, MTS-Free survival, CSS, and OS were 31.7% (95% CI: 26.33-37.1), 66.3% (95% CI: 60.4-72.1), 97.7% (95% CI: 95.5-99.8), and 95.3% (95% CI: 92.4-98.1), respectively. MTS-free survival was significantly associated with PSA persistence ($p<0.01$), higher ISUP at RP ($p=0.01$), but not with an increased number of positive nodes ($p=0.08$). In the multivariable analysis, PSA persistence emerged as an independent predictor of BCR (OR 51.8, 95% CI 12.2-219.2), Exit from Obs (OR 8.5, 95% CI 4.4-16.5), and Systemic progression (OR 3.0, 95% CI 1.771-4.971).
b) When including Obs and aRT groups, at multivariable analyses, ≥3 positive nodes (HR 2.03, 95% CI 1.22-3.37; $p=0.006$) and ISUP 5 were associated (HR 1.92, 95% CI 1.15-3.18; $p=0.01$) with an increased all-cause mortality. Based on pT stage, ISUP and positive nodes, a model comprising three risk categories was created. In men with no PSA persistence, seven-year OS rates were comparable for low and intermediate risk categories (both $p>0.2$) but improved for aRT versus Obs and eventual early sRT in the high-risk group (aRT 91.7%, 95% CI 87.3-96.3 vs. 82.7%, 95% CI 74.4-91.9; $p=0.01$. aRT confirmed its protective effect on mortality risk only in high-risk patients (HR 0.5, 95% CI 0.3-0.9, $p=0.04$) in multivatiable models.Results were comparable when including men with PSA persistence.

iv) Patients with cN+ on PSMA PET/CT had an increased risk of systemic progression (52.9% vs. 13.6% cN0 PSMA PET/CT vs. 21.5% cN0 at conventional imaging; $P < .01$). This held true at multivariable analysis: (HR 6.184, 95% CI: 3.386-11-295; $P < .001$). No relevant results were found for choline PET/CT.

v) Nodal yield was 17.3 (5.8 SD) per case. PET/CT images revealed focal uptake (TBR 13.6) in a metastatic node, and no uptake or diffuse in negative nodes (TBR range: 1-5.3). Intraoperative PET/CT images clearly showed negative margins in two patients, whereas the results were uncertain in a locally advanced case.

Conclusions

i) Existing single- and multi-institutional cohorts show pN+ PCa have a relatively aggressive PCa but yield promising oncological control and survival rates with a significant proportion of patients remaining disease free. Different management strategies are available including initial Obs, aRT and/or aADT. The level of evidence for the management of pN1 patients is still low with only one RCTs specifically designed for this setting. Registry based studies mirror the outcomes of single- or multi-institutional series in terms of pN+ oncological outcomes and variety of management strategies.

ii) The urological community has a generally satisfactory level of awareness regarding pN+ PCa and consider pN+ disease as a complex category, without gold standard management and increasingly relying on PSMA-PET.

iii) Obs is feasible and has good prognosis on the intermediate term in selected men but patients with PSA persistence are not optimal candidates due to worse outcomes.

aRT has no OS benefit compared to Obs with or without early sRT. However, when risk stratifying men based on clinical variables those in the high risk category benefit from aRT whilst the others do not and may be spared the morbidity of aRT. We created a risk model to guide clinical decision making in this setting.

iv) Men with PSMA PET/CT positive nodes being confirmed at final pathology after surgery may yield a higher risk of systemic progression compared to those with a no nodal uptake at pre-operative PSMA.

v) PET/CT imager use intraoperatively is a promising option and appears safe and feasible.

Further studies are needed to confirm our findings on larger cohorts, ideally in a randomized context whilst larger prospective series are awaited to assess potential impact of novel intraoperative technologies.