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Identifying the Optimal Candidate for Salvage Lymph Node Dissection for Nodal Recurrence of Prostate Cancer: Results from a Large, Multi-institutional Analysis

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.09.009.

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Abstract

Background: Salvage lymph node dissection (SLND) represents a possible treatment option for prostate cancer patients affected by nodal recurrence after local treatment. However, SLND may be associated with intra- and postoperative complications, and the oncological benefit may be limited to specific groups of patients.

Objective: To identify the optimal candidates for SLND based on preoperative characteristics.

Design, setting, and participants: The study included 654 patients who experienced prostate-specific antigen (PSA) rise and nodal recurrence after radical prostatectomy (RP) and underwent SLND at nine tertiary referral centers. Lymph node recurrence was documented by positron emission tomography/computed tomography (PET/CT) scan using either ^{11}C-choline or ^{68}Ga-labeled prostate-specific membrane antigen ligand.

Intervention: SLND.

Outcome measurements and statistical analysis: The study outcome was early clinical recurrence (eCR) developed within 1 yr after SLND. Multivariable Cox regression analysis was used to develop a predictive model. Multivariable-derived coefficients were used to develop a novel risk calculator. Decision-curve analysis was used to evaluate the net benefit of the predictive model.

Results and limitations: Median follow-up was 30 (interquartile range, 16–50) mo among patients without clinical recurrence (CR), and 334 patients developed CR after SLND. In particular, eCR at 1 yr after SLND was observed in 150 patients, with a Kaplan-Meier probability of eCR equal to 25%. The development of eCR was significantly associated with an increased risk of cancer-specific mortality at 3 yr, being 20% versus 1.4% in patients with and without eCR, respectively ($p < 0.0001$). At multivariable analysis, Gleason grade group 5 (hazard ratio [HR]: 2.04; $p < 0.0001$), time from RP to PSA rising (HR: 0.99; $p = 0.025$), hormonal therapy administration at PSA rising after RP (HR: 1.47; $p = 0.0005$), retroperitoneal uptake at PET/CT scan (HR: 1.24; $p = 0.038$), three or more positive spots at PET/CT scan (HR: 1.26; $p = 0.019$), and PSA level at SLND (HR: 1.05; $p < 0.0001$) were significant predictors of CR after SLND. The coefficients of the predictive model were used to develop a risk calculator for eCR at 1 yr after SLND. The discrimination of the model (Harrel's C index) was 0.75. At decision-curve analysis, the net benefit of the model was higher than the "treat-all" option at all the threshold probabilities.

Conclusions: We reported the largest available series of patients treated with SLND. Roughly 25% of men developed eCR after surgery. We developed the first risk stratification tool to identify the optimal candidate to SLND based on routinely available preoperative characteristics. This tool can be useful to avoid use of SLND in men more likely to progress despite any imaging-guided approach.

Patient summary: The risk of early recurrence after salvage lymph node dissection (SLND) was approximately 25%. In this study, we developed a novel tool to predict the risk of early failure after SLND. This tool will be useful to identify patients who would benefit the most from SLND from other patients who should be spared from surgery.

Keywords

Prostatic neoplasms; Neoplasm recurrence; Positron emission tomography; computed tomography; Lymph node excision; Salvage therapy

1. Introduction

Approximately 25% of patients with biochemical recurrence (BCR) after radical prostatectomy (RP) experience clinical progression at long-term follow-up [1,2]. However, the outcome of these patients is not invariably poor, varying significantly according to the site and the extent of recurrence [3].

In this context, the increasing use of positron emission tomography/computed tomography (PET/CT) has led to a shift towards early detection of low-volume metastatic prostate cancer (PCa) (eg, isolated nodal recurrences) that, in turn, has contributed to a shift in the treatment paradigm of these patients [4,5]. Recently, the European Association of Urology guidelines have indeed introduced salvage lymph node dissection (SLND) as a possible treatment option for men with nodal recurrence after local treatment [6]. The rationale of this approach is based on the evidence that men with nodal recurrences have better prognosis compared to their counterparts with bone or visceral metastasis [7–10]. However, considering the high risk of clinical relapse after SLND [11–16], one of the main endpoints would be represented by the delay of systemic treatment administration, as recently shown in a phase 2 trial [17]. Despite the possible benefit on hormonal therapy (HT)–free survival, it is currently unknown whether SLND is associated with better cancer control compared to standard treatments. This is mainly due to the lack of large, prospective, randomized trials focusing on hard clinical endpoints. While waiting for robust evidence, it would be important to identify patients who may have good outcomes after SLND [18] and to spare the surgical intervention and its possible related side effects in those patients who invariably progress despite the use of SLND [19]. As such, the identification of the optimal candidate for SLND is of utmost importance to maximize cancer control and to avoid overtreatment. We thus aimed at identifying the optimal candidate for SLND based on a large, multi-institutional series of patients treated for node-only recurrent PCa detected at PET/CT scan after RP.

2. Materials and methods

2.1. Patient population

Institutional Review Board approval was obtained for data sharing through the different centers. We identified 840 patients who experienced prostate-specific antigen (PSA) rise and nodal recurrence after RP and underwent SLND at nine tertiary referral centers by expert surgeons between 2002 and 2016. Lymph node recurrence was documented by PET/CT scan using either ^{11}C-choline or ^{68}Ga-labeled prostate-specific membrane antigen (^{68}Ga-PSMA)

ligand. All patients were preoperatively staged with abdominal CT scan and bone scan using technetium Tc 99m methylene diphosphonate (Tc 99m MDP) to exclude any other sites of recurrence.

Patients with missing information for Gleason grade group (n = 29), site of positive uptake at PET/CT scan (n = 21), number of positive spots at PET/CT scan (n = 6), HT administration before SLND (n = 48), PSA level at SLND (n = 1), PSA level after SLND (n = 15), and follow-up data (n = 30) were excluded. Furthermore, 36 patients received targeted SLND to the positive nodes at PET/CT scan only. These patients were excluded because of the high risk of missed lymph node metastases [13,20]. These selection criteria yielded 654 evaluable individuals with complete clinical, pathological, and follow-up data.

2.2. Surgical technique

The surgical technique was previously described [20] and was consistent through the different centers. In brief, pelvic SLND consisted of the excision of external iliac, obturator, internal iliac, common iliac, and presacral nodes. The distal limit of the dissection was represented by the femoral canal, whereas the proximal limit consisted of the aortic bifurcation. All fibro-fatty tissue within the obturator fossa was removed to completely skeletonize the obturator nerve. The medial and the lateral limits of the dissection consisted of the peri-vesical fat and the pelvic sidewall, respectively. At the discretion of the surgeon, intraoperative frozen section analysis of the common iliac nodes was performed. When positive, lymphadenectomy was extended to the retroperitoneum, based on the high probability of retroperitoneal lymph node metastasis [21].

Retroperitoneal SLND consisted of the excision of all nodal tissue located between the renal artery (cranially) and the aortic bifurcation (caudally). Lateral limits consisted of the right ureter (on the right) and the left ureter (on the left). All nodal specimens were mapped according to their anatomic location and sent for pathological assessment in multiple packages.

2.3. Follow-up

Follow-up consisted of PSA testing 1 mo after surgery; 3, 6, 9, and 12 mo after SLND; and biannually thereafter. Postoperative ^{11}C-choline PET/CT scan and eventual bone scan using Tc 99m MDP were performed in case of PSA rising after SLND. The administration of additional treatments after SLND was left at the discretion of the surgeon.

2.4. Variable definition

Data consisted of variables related to RP; SLND, pretreatment; and SLND, post-treatment.

1. RP: age at RP (years), preoperative PSA level (nanograms per milliliter), primary tumor (pT) stage (pT2 vs pT3a vs ≥pT3b), Gleason grade group (≤3 vs 4 vs 5), surgical margin status (negative vs positive), lymph node (pN) stage (pN0 vs pN1 vs pNx), number of lymph nodes removed, number of positive nodes, first PSA level at 1 mo after RP (nanograms per milliliter; PSA persistence was defined as a serum concentration ≥0.1 ng/ml at 1 mo after RP [22]), adjuvant HT

(no vs yes; type and duration of HT), and adjuvant RT (no vs yes; dose and field of RT).

2. SLND, pretreatment: time from RP to PSA rising (months), HT administration at the time of PET/CT scan (no vs yes; type and duration of HT), PET/CT tracer (^{11}C-choline vs ^{68}Ga-PSMA), site of positive uptake at PET/CT scan (pelvic vs retroperitoneal vs both), number of positive spots at PET/CT (1 vs 2 vs 3 vs ≥4), age at SLND (years), and PSA level at SLND (nanograms per milliliter).

3. SLND, post-treatment: number of lymph nodes removed, number of positive nodes, PSA level at 1 mo after SLND (nanograms per milliliter), and PSA difference (PSA pre-SLND and PSA post-SLND).

2.5. Outcome definition

The primary outcome of the study was early clinical recurrence (eCR) after SLND that was defined as positive imaging in presence of a rising PSA within 12 mo after surgery. Such a definition of eCR was derived by the control group of a randomized phase 2 trial testing the role of metastasis-directed therapy (including SLND) in oligometastatic recurrent PCa [17]. Furthermore, in the recently published Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients (ICECaP) study, metastasis-free survival was a strong surrogate for overall survival for localized pCa [23]. Follow-up time consisted of the time between SLND and clinical recurrence or last follow-up. Secondary outcomes consisted of BCR after SLND (defined as PSA level ≥0.2 ng/ml and rising), and HT-free survival.

2.6. Statistical analyses

Statistical analyses consisted of three main steps. First, Kaplan-Meier analysis was used to assess clinical recurrence (CR), BCR, and HT-free survival after SLND. Second, multivariable Cox regression analyses were used to predict CR after SLND. Predictors consisted of Gleason grade group (≤4 vs 5), time from RP to PSA rising (months), HT administration at the time PET/CT scan (no vs yes), site of positive imaging (pelvis vs retroperitoneum ± pelvis), number of positive spots at PET/CT scan (one or two vs three or more), and PSA level at SLND (nanograms per milliliter). The discrimination of the model was tested using Harrel's C index. The ten-fold cross-validation was used to correct Harrell's C index for overfit. The predictive model coefficients were used to calculate the risk of eCR at 1 yr after SLND for each patient and to develop the corresponding risk calculator. Third, decision-curve analysis was used to evaluate the net benefit of the predictive model.

All statistical analyses were performed using Stata version 12.0 (StataCorp LP, College Station, TX, USA).

3. Results

Descriptive characteristics of patients are illustrated in Tables 1–3. At RP, 466 (71%) patients were pN0, 104 (16%) were pN1, and 84 (13%) were pNx (Table 1). At PET/CT scan (Table 2), 534 (82%) patients had pelvic uptake. Of these, 442 (82.7%) received

pelvic SLND only and 92 (17.3%) received both pelvic and retroperitoneal SLND. By contrast, 62 patients (9%) had retroperitoneal uptake and 58 patients (9%) had both pelvic and retroperitoneal uptake. All patients with retroperitoneal involvement at PET/CT scan received both pelvic and retroperitoneal SLND. Median (interquartile range [IQR]) number of lymph nodes removed at SLND was 26 (15–38). The number of positive nodes at SLND was zero, one, two, and three or more in 62 (9%), 150 (23%), 92 (14%), and 350 (54%) patients, respectively (Table 3).

Surgical route consisted of open, laparoscopic, and robotic technique in 572 (87%), 6 (1%), and 76 (12%) patients, respectively. Intra- and postoperative complications of SLND were illustrated in Supplementary Table 1. Type of intraoperative complications were reported, and Clavien-Dindo classification was considered for postoperative complications.

Median follow-up among patients who did not develop CR was 30 (IQR, 16–50) mo; 334 patients developed CRafter SLND. CR-free survival, BCR-free survival, and HT-free survival are illustrated in Figures 1, 2, and 3, respectively. In particular, eCR at 1 yr after SLND was observed in 150 patients, with a Kaplan-Meier probability of eCR equal to 25% (95% confidence interval [CI]: 20–30). The development of eCR was significantly associated with increased risk of 3-yr cancer-specific mortality (Fig. 4), being 20% versus 1.4% in men with and without eCR, respectively ($-p < 0.0001$).

At multivariable Cox regression analysis, Gleason grade group 5 (hazard ratio [HR]: 2.04; 95% CI: 1.66–2.50; $p < 0.0001$), time from RP to PSA rising (HR: 0.99; 95% CI: 0.98–0.99; $p = 0.025$), HT administration at PSA rising after RP (HR: 1.47; 95% CI: 1.19–1.82; $p = 0.0005$), retroperitoneal uptake at PET/CT scan (HR: 1.24; 95% CI: 1.01–1.52; $p = 0.038$), three or more positive spots at PET/CT scan (HR: 1.26; 95% CI: 1.05–1.61; $p = 0.019$), and PSA level at SLND (HR: 1.05; 95% CI: 1.04–1.07; $p < 0.0001$) were significant predictors of CR after SLND (Table 4).

The coefficients of the predictive model were used to develop a risk calculator (Supplementary data) for eCR at 1 yr after SLND. The discrimination of the model (Harrel's C index) was 0.75. Decision-curve analysis illustrated the net benefit of the model, which was higher than the "treat-all" option at all the threshold probabilities (Fig. 5).

4. Discussion

In this study, we aimed at identifying the optimal candidate for SLND among men with node-only recurrent PCa after RP based on the largest available series. Although this surgical approach has now been included in the currently available guidelines as a possible treatment option for these men, it is currently unknown which patient could benefit the most from this treatment. Such void is due to two main reasons: (i) the lack of large phase 3 trials testing the role of SLND compared to standard management, and (ii) unavailability of any risk prediction model able to assess the outcomes of men treated with SLND. Men with node recurrent PCa have indeed heterogeneous outcomes according to clinical and pathological characteristics. Although some of these patients are affected by a systemic disease upfront leading to early recurrence after SLND, others have a true oligo-recurrent

disease. This has, in turn, significant therapeutic implications. Indeed, while in the first patient group any metastasis-directed therapy might be of limited value, in the second group such an approach might be beneficial, allowing at least to postpone the use of systemic treatments. In this study, we hypothesized that patients with lymph node recurrence from PCa can be accurately stratified according to their risk of eCR after SLND, thus allowing for accurate selection of the optimal candidate for SLND. Our results confirmed our initial hypothesis, as we were able to develop the first risk prediction model for eCR after SLND based on the largest multi-institutional series. Several facets of our findings deserve attention.

First, we identified clinical and pathological predictors of eCR after SLND that formed the basis of a novel and accurate (area under the curve, 75%) risk prediction model (Supplementary data). This risk calculator can be used to assess individual risk of early failure after SLND, having the predictive model a higher clinical net-benefit compared to the "treat-all" option at decision curve analysis. The endpoint of our study was eCR based on the assumption that men with eCR are those likely to have systemic, disseminated disease already at the time of SLND. The definition of eCR was derived from the control group of a recent prospective randomized phase 2 trial focused on men with oligo-recurrent PCa [17]: in the observational arm, patients had a median time to progression of 13 mo. Although men with bone and visceral metastases also were included in that trial, we postulated that any metastasis-directed therapy such as SLND should at least prolong the onset of clinical progression of oligo-recurrent disease. This is important, given the protracted natural history of men with node-recurrent-only disease. Our model can be used to evaluate the individual patient risk of eCR and, in turn, to optimize patient selection for SLND. For example, a patient with two positive spots detected at PET/CT in the pelvis, a PSA of 2.2 ng/ml at 36 mo after RP with Gleason 4 + 3 without any previous hormonal manipulation showed a risk of eCR of 15%. Conversely, a man with three positive spots detected at PET/CT in the para-aortic nodes, a PSA of 4.8 ng/ml at 24 mo after RP with a Gleason 4 + 5 with previous hormonal manipulation showed a risk of eCR of 59%. Although risk of eCR for men with isolated nodal recurrence managed conservatively is unknown in our study due to the lack of a control group, we argue that SLND would be hardly justifiable in men with high risk of early CR for the presence of concomitant systemic disease likely undetected by imaging. Therefore, the impact of any imaging-guided therapy may be highly diluted in this patient group. Conversely, men with lower risk of eCR are those in whom SLND may be associated with higher impact on patient outcomes. However, whether favorable outcomes were due to the impact of SLND or simply related to disease biology is currently unknown and cannot be answered by our study, given the lack of a control group not receiving SLND.

Second, our results are in line with those obtained by metastasis-directed therapy in the above-mentioned phase 2 randomized trial of oligo-recurrent PCa [17]. In our study, median time to progression after SLND was 18 mo, comparable to the time reported by Ost et al in the group of men randomized to metastasis-directed therapy. Therefore, despite the lack of a control group, our results indicate the possible role of SLND in delaying further clinical progression in men with node-only PCa recurrence. Indeed, at 3-yr follow-up, approximately one in four patients was free from both BCR and HT. Interestingly, in the study by Ost et al, use of metastasis-directed therapy had comparable effect on HT-free survival in men with

nodal versus non-nodal metastases, opening new perspectives in future large phase 3 trials testing the role of metastasis-directed therapy in the entire oligo-recurrent setting.

Third, our results seem to confirm previously identified prognostic factors for SLND reported in more limited series, such as site of nodal involvement at imaging, PSA value at SLND, and the number of positive spots at PET/CT [11–16,20]. However, in addition to previous studies, we were able to combine these predictors into the first risk prediction model using eCR as endpoint and developed in the largest available series of SLND. Our results reiterate the importance of a multivariable risk assessment of these patients, an assessment that should consider several clinical and pathological variables to optimize risk assessment and patient selection. Finally, our results are hypothesis generating and can be used to select the optimal candidate for SLND to be included future prospective randomized trials.

Despite several strengths, our study is not devoid of limitations. First, no control group of patients receiving standard of care was included. Therefore, based on these results, it is not possible to compare oncological outcomes with patients treated with standard management. This procedure is still experimental, and patients should be informed accordingly. Second, the lack of standardized post-RP management may represent a limitation of this study. But it reflects the real-life clinical scenarios, where patients with nodal recurrence have extremely heterogeneous urological and oncological histories. Therefore, the simple exclusion of patients receiving (or not receiving) androgen deprivation therapy and/or RT may represent an additional selection bias. For this reason, we decided to include all patients treated with SLND and to use multivariable analysis to adjust for these specific factors. Third, although all men were surgically treated at high-volume centers, given the retrospective nature of our study diagnostic biases could have been introduced from possible differences in surgical templates among surgeons. Fourth, not all patients received the same imaging protocols, since either ^{11}C-choline or ^{68}Ga-PSMA was used as a tracer for PET/CT scan that could be associated with different diagnostic performances. Finally, central pathological review of the specimens was not conducted in this multi-institutional study.

5. Conclusions

We reported the largest available series of patients treated with SLND. Roughly 25% of men developed eCR after surgery. We developed the first risk stratification tool to identify the optimal candidate to SLND based on routinely available preoperative characteristics. This tool can be useful to avoid use of SLND in men more likely to progress despite any imaging-guided approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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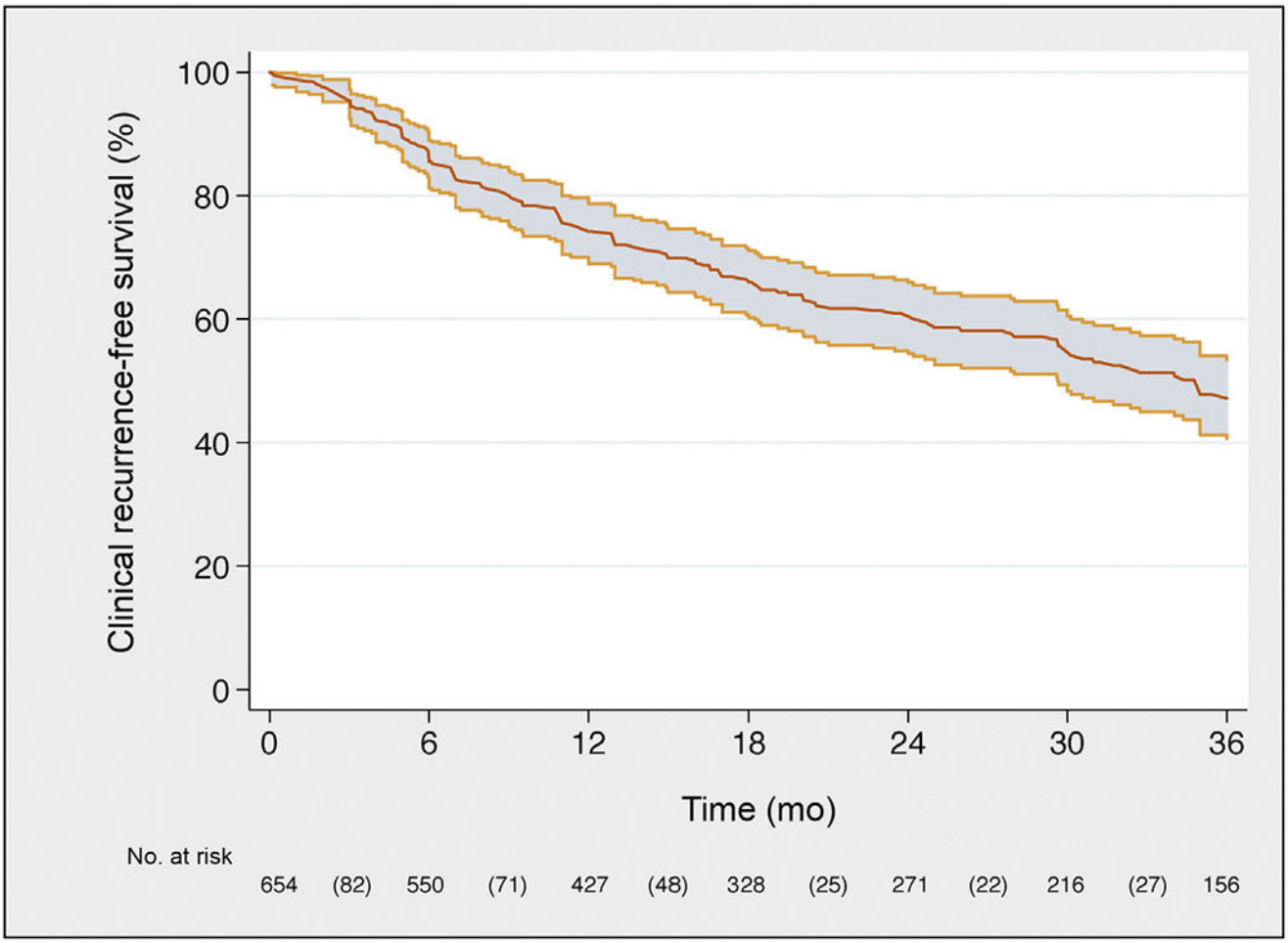

Fig. 1 –.
Kaplan-Meier plot depicting clinical recurrence-free survival in the overall population.

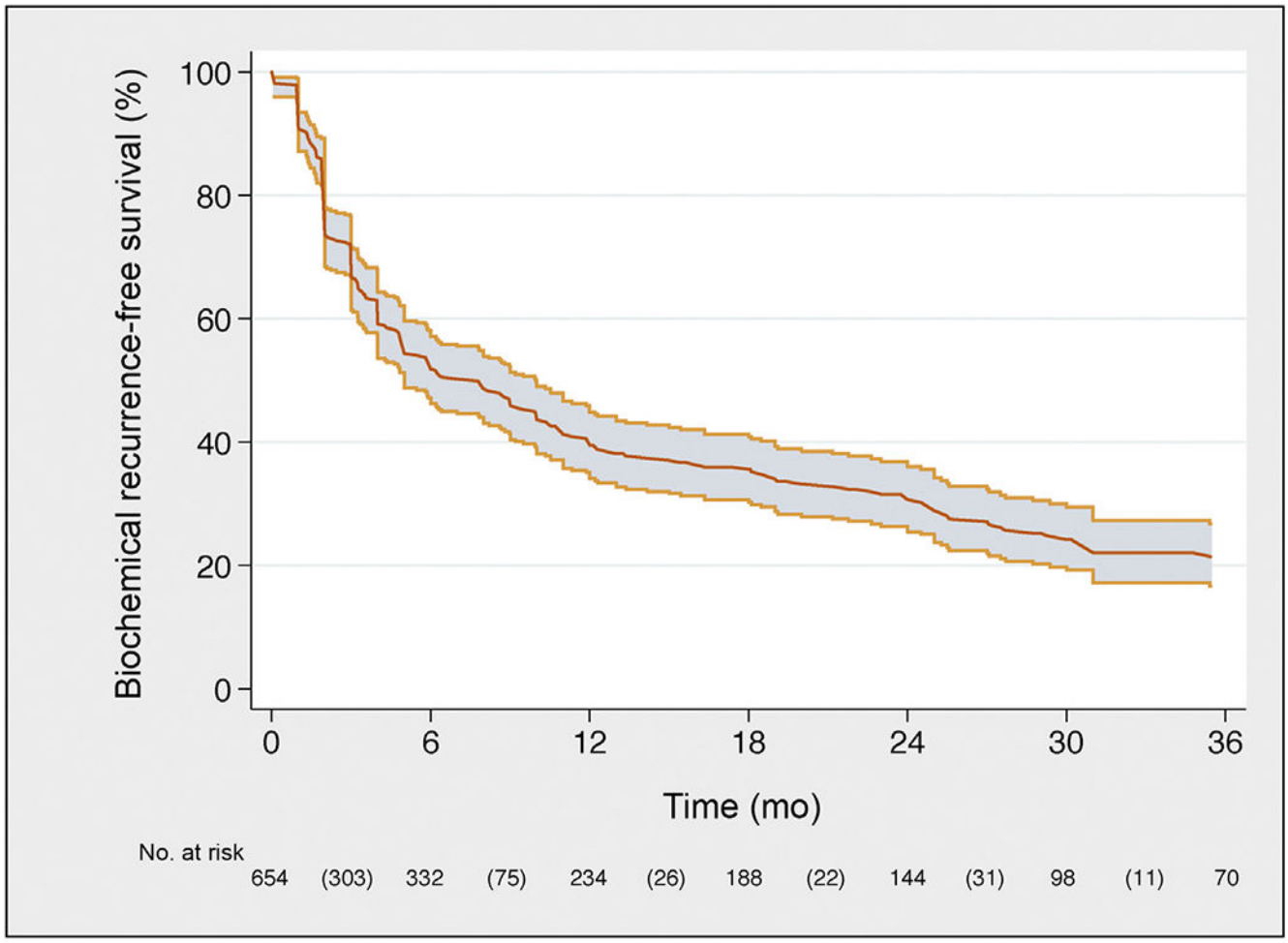

Fig. 2 –.
Kaplan-Meier plot depicting biochemical recurrence-free survival in the overall population.

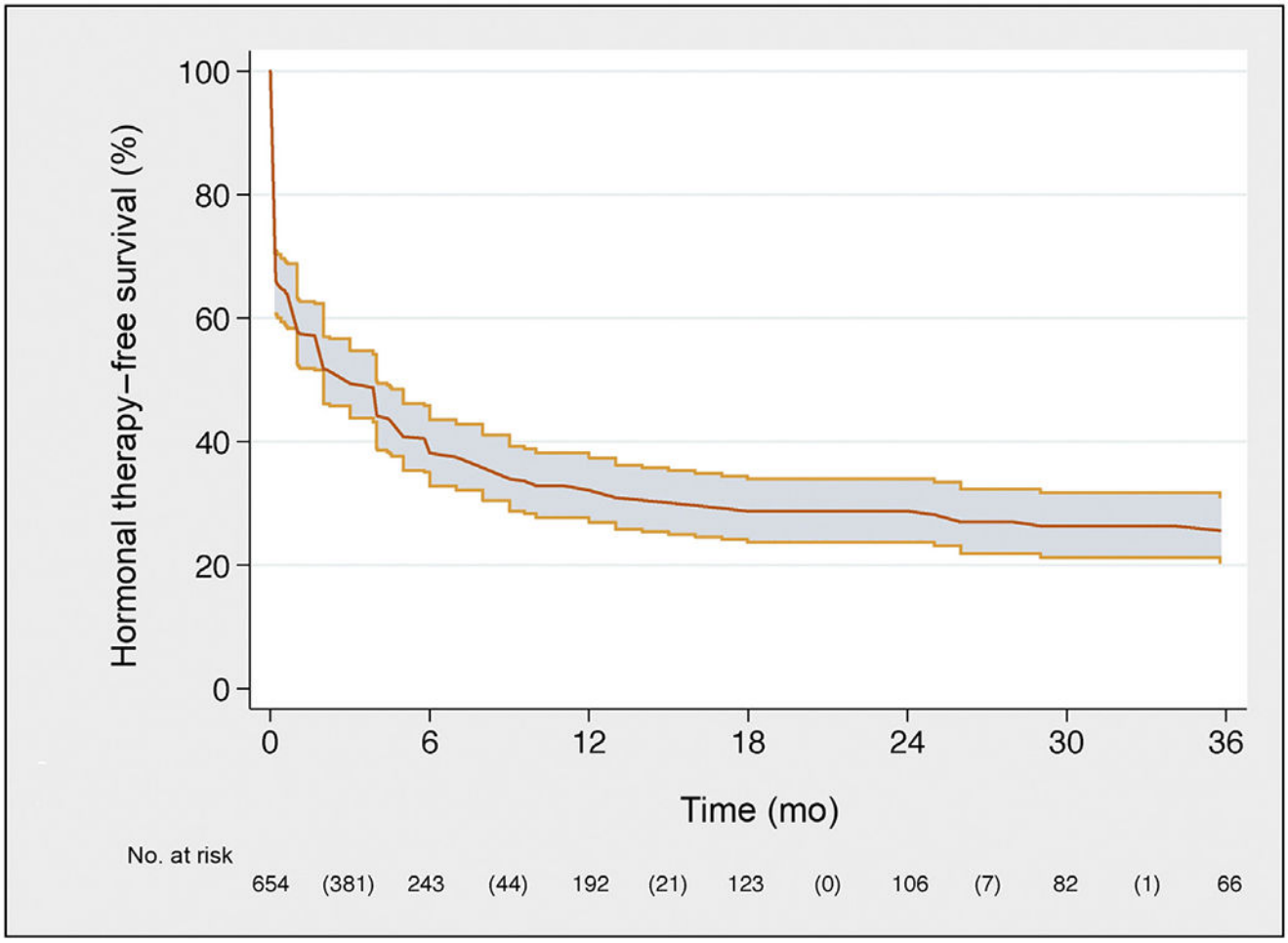

Fig. 3 –.
Kaplan-Meier plot depicting hormonal therapy-free survival in the overall population.

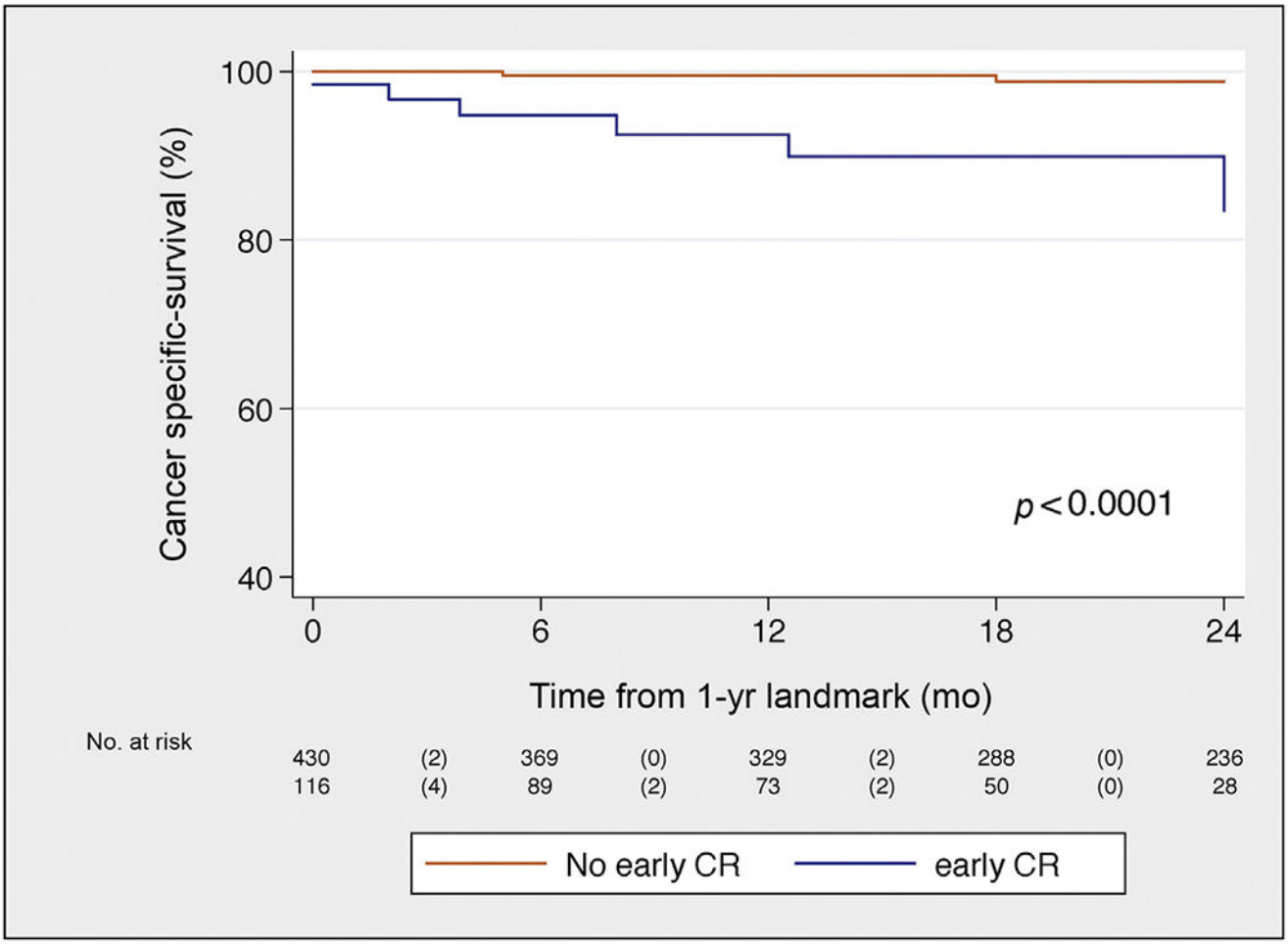

Fig. 4 –.

Kaplan-Meier plot depicting cancer-specific mortality, stratified in two groups: patients who developed early clinical recurrence versus patients who did not.

CR = clinical recurrence.

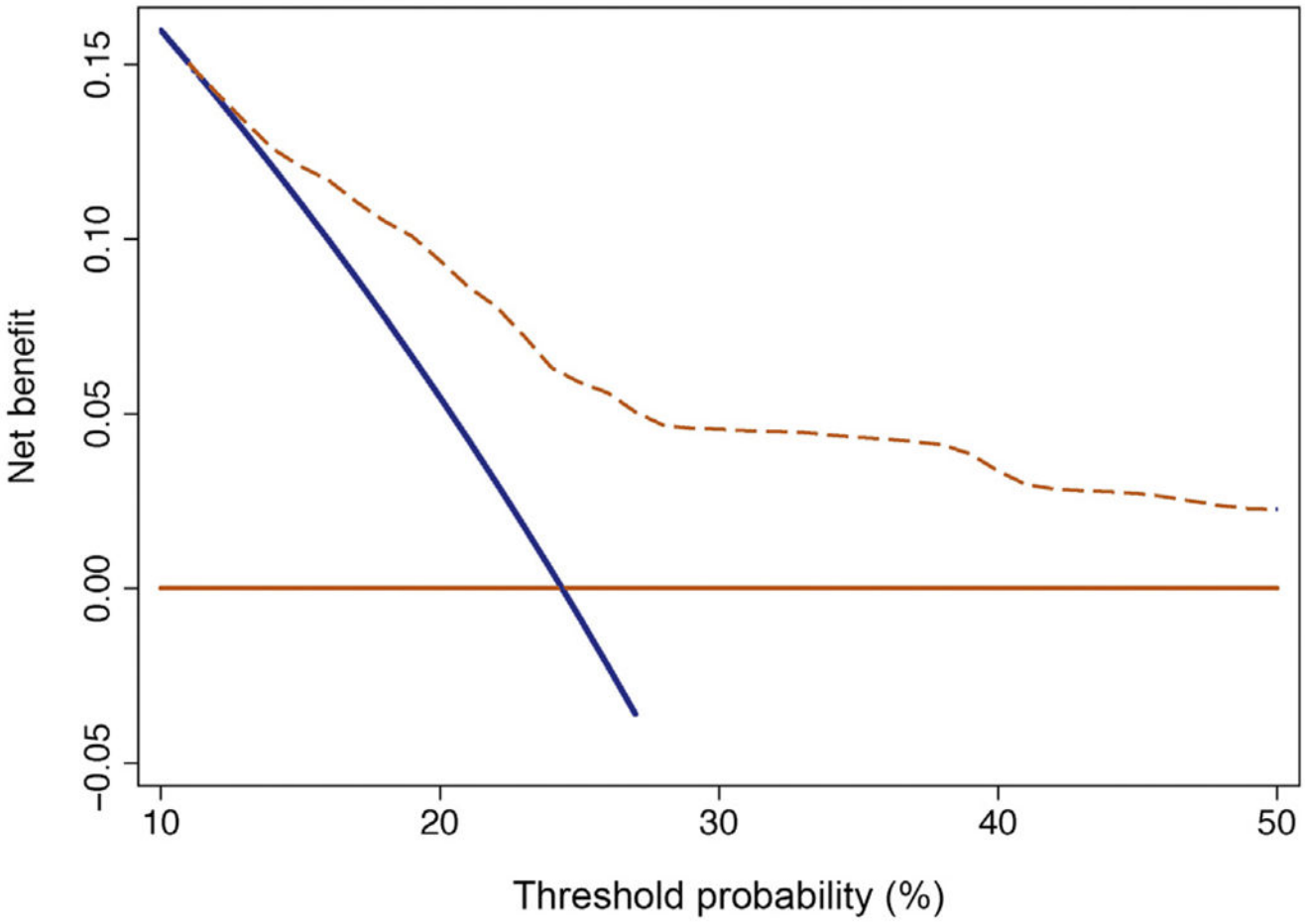

Fig. 5 –.
Decision-curve analysis assessing the net benefit of the model.

Table 1 –

RP characteristics of 654 patients treated with salvage lymph node dissection for nodal recurrence of prostate cancer

Variable	Overall population (*n* = 654; 100%)
Age at RP, yr	59 (55–65)
Pre-RP PSA level, ng/ml	8.4 (5.9–13.0)
Pathologic T stage, *n* (%)	
pT2	210 (32)
pT3a	214 (33)
pT3b	214 (33)
Unknown	16 (2)
Surgical margins, *n* (%)	
Negative	396 (61)
Positive	232 (35)
Unknown	26 (4)
Gleason grade group, *n* (%)	
≤3	22 (3)
4	352 (54)
5	280 (43)
Pathologic N stage, *n* (%)	
pN0	466 (71)
pN1	104 (16)
pNx	84 (13)
Lymph nodes removed at RP	8 (5–14)
Undetectable PSA after RP, *n* (%)	
No	254 (39)
Yes	284 (43)
Unknown	116 (18)
Post-RP radiation therapy, *n* (%)	
No	258 (39)
Yes	396 (61)
Type of radiation therapy, *n* (%)	
No	258 (39)
Adjuvant	56 (9)
Salvage for PSA rising	296 (45)
Salvage for PSA persistence	44 (7)

PSA = prostate-specific antigen; RP = radical prostatectomy.

All values are medians (interquartile range) or frequencies (proportions).

Table 2 –

Pre-SLND characteristics of 654 patients treated with salvage lymph node dissection for nodal recurrence of prostate cancer

Variable	Overall population (*n* = 654; 100%)
Time from RP to PSA rising, mo	19 (4–44)
HT administration at PSA rising, *n* (%)	
No	538 (82)
Yes	116 (18)
Type of PET/CT tracer, *n* (%)	
^{11}C-Choline	460 (70)
^{68}Ga-PSMA	194 (30)
Positive sites at PET/CT scan, *n* (%)	
Pelvic	534 (82)
Retroperitoneal	62 (9)
Both	58 (9)
Positive spots at PET/CT scan, *n* (%)	
1	332 (51)
2	150 (23)
3	112 (17)
≥4	60 (9)
Age at SLND, yr	66 (60–70)
PSA at SLND, ng/ml	2.1 (1.0–4.0)

HT = hormonal therapy; PET/CT = positron emission tomography/computed tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RP = radical prostatectomy; SLND = salvage lymph node dissection.

All values are medians (interquartile range) or frequencies (proportions).

Table 3 –

Post-SLND characteristics of 654 patients treated with salvage lymph node dissection for nodal recurrence of prostate cancer

Variable	Overall population (*n* = 654; 100%)
Lymph nodes removed at SLND	26 (15–38)
Positive lymph nodes at SLND, *n* (%)	
0	62 (9)
1	150 (23)
2	92 (14)
≥3	350 (54)
PSA after SLND, ng/ml	0.3 (0.0–1.0)
PSA difference (after–pre), ng/ml	−1.4 (−2.8 to−0.3)
PSA response after SLND	
(<0.2 ng/ml), *n* (%)	
No	368 (56)
Yes	286 (44)
Undetectable PSA after SLND	
(<0.1 ng/ml), *n* (%)	
No	456 (70)
Yes	198 (30)

PSA = prostate-specific antigen; SLND = salvage lymph node dissection.

All values are medians (interquartile range) or frequencies (proportions).

Table 4 –

Multivariable Cox regression analysis predicting clinical recurrence after SLND in 654 patients treated for nodal recurrence of prostate cancer

Predictor	HR	95% CI	*p* value
Gleason grade group			
≤4	1.00	Ref.	–
5	2.04	1.66–2.50	<0.0001
Time from RP to PSA rising, per 6 mo	0.98	0.96–0.99	0.025
HT administration at the time of PET/CT scan			
No	1.00	Ref.	–
Yes	1.47	1.19–1.82	0.0005
Retroperitoneum involvement at PET/CT scan			
No	1.00	Ref.	–
Yes	1.24	1.01–1.52	0.038
Positive spots at PET/CT scan			
≤2	1.00	Ref.	–
≥3	1.26	1.05–1.61	0.019
PSA at SLND, ng/ml	1.05	1.04–1.07	<0.0001

CI = confidence interval; HR = hazard ratio; HT = hormonal therapy; PET/CT = positron emission tomography/computed tomography; PSA = prostate-specific antigen; Ref. = reference; RP = radical prostatectomy; SLND = salvage lymph node dissection.