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Survival Benefit of Radical Prostatectomy in Lymph Node–Positive Patients with Prostate Cancer

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Abstract

Background: Positive lymph node (LN) status is considered a systemic disease state. In prostate cancer, LN-positive diagnosis during pelvic LN dissection (PLND) potentially leads to the abandonment of radical prostatectomy (RP).
Objective: To compare the overall survival (OS) and relative survival (RS; as an estimate for cancer-specific survival) in LN-positive patients with or without RP.
Design, setting, and participants: Between 1988 and 2007, a total of 35 629 men with prostate cancer were identified at the Munich Cancer Registry; of those, 1413 patients had positive LNs.
Intervention: Of these 1413 LN-positive patients, prostatectomy was abandoned in 456 LN-positive patients, whereas 957 underwent RP despite the LN-positive finding.
Measurements: Crucial analyses are based on 938 LN-positive patients (688 with RP and 250 without RP) with complete data regarding age, grade, and prostate-specific antigen (PSA). OS (Kaplan-Meier estimates) and RS are presented, and Cox regression analysis was used to show the influence of predictors such as clinical stage, age at surgery, number of positive LNs, PSA level, grade, and extent of surgery.
Results: Median follow-up was 5.6 yr. OS of patients at 5 yr and 10 yr was 84% and 64%, respectively, with RP and was 60% and 28%, respectively, with aborted RP. The RS of patients at 5 yr and 10 yr was 95% and 86%, respectively, with RP and was 70% and 40%, respectively, with abandoned surgery. There was an imbalance, however, in the number of positive LNs: 17.2% with RP had four or more positive nodes versus 28% in the patient group without RP. In the multivariate model, RP was a strong independent predictor of survival (hazard ratio: 2.04 [95% confidence interval, 1.59–2.63; $p < 0.0001$]).
Conclusion: LN-positive patients with complete RP had improved survival compared to patients with abandoned RP. These results suggest that RP may have a survival benefit and the abandonment of RP in node-positive cases may not be justified.

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1. Introduction

Radical prostatectomy (RP) is commonly accepted as standard therapy for early stage prostate cancer [1–4]. Although multiple investigations have demonstrated that RP is also a valid option for patients with locally advanced disease [5,6], RP is often abandoned in cases with positive lymph nodes (LNs). Prostate cancer patients who are LN positive are considered to have a systemic disease with poor prognosis and are often treated with hormonal therapy [7] and/or radiotherapy (RT).

Interestingly, few studies have shown reasonable cancer-specific survival (CSS) of patients with histologically diagnosed pelvic LN metastases who received RP [8–12]. Furthermore, not all patients with nodal disease are at the same risk of cancer-specific death. Patients with minimal nodal disease have improved survival and may benefit from RP [10,11].

Today, most surgeons do not routinely perform frozen section analysis of pelvic LNs or abandon RP in the case of an LN-positive finding. The comparison of CSS in LN-positive patients who receive complete RP versus abandoned RP is often compromised by small populations and short follow-up. In this study, we analyzed overall survival (OS) and relative survival (RS) in LN-positive patients with or without RP.

2. Materials and methods

2.1. Data collection

The Munich Cancer Registry (MCR) was established in 1978. Initially, the MCR cooperated with the two university hospitals in Munich, Germany, and since 1988, collaborations have extended to all city hospitals and the district of Munich, a region of about 2.3 million inhabitants. The MCR was enlarged to 3.8 million people in 2002 and to 4.5 million in 2007. With an incidence rate of 80 per 100 000 people (world standard), the MCR observes a high population-based incidence of prostate cancer patients in Germany, which is about 75% of the incidence in the United States.

Data about primary disease characteristics such as TNM stage, histology, World Health Organization (WHO) grade, and therapy were prospectively collected from MCR-affiliated hospitals using tumor-specific forms. The extent of the lymphadenectomy cannot be provided, and Gleason score is only documented since the year 2000. Additionally, all pathologic reports have been archived since 1994 and were used as supplementary information. Since 1978, the life status of patients with a cancer diagnosis has been maintained systematically through death certificates and the inhabitants' registration offices. Thus, active follow-up data are available for about 90% of all cases.

2.2. Patients

Since 1988, 35 629 patients with histologically confirmed prostate cancer were prospectively registered in the database of the MCR. The year 1988 was selected a priori as a cutoff point because therapy regimes have changed since the 1980s and recruitment was approximately population based in the MCR. Patients with neoadjuvant therapy (n = 392*) and evidence of a previous malignant tumor (n = 2958*) or another synchronous malignant tumor (n = 1002*) were excluded from the analyses (*overlapping specifications are possible for these samples). Patients of a district where the inhabitants' registration office did not provide life status were also excluded (n = 3924; 11%). Analyses were therefore performed on 27 956 patients with primary prostate cancer diagnosed between 1988 and 2007. Of these 27 956 patients, 13 805 had information on their LN status, and 1413 (10.2%) patients were diagnosed as LN positive during pelvic LN dissection (PLND) and underwent completed or abandoned RP. The majority of patients received adjuvant or salvage hormonal ablation therapy. The presented adjuvant data, however, only reflect information about adjuvant treatment that was given or that began during the hospital stay.

2.3. Statistical analysis

The MCR organizes data in an Oracle database. Statistical analyses were run in SAS (Statistical Analysis System v.8.2). Frequency data were analyzed using the χ^2 test or the Fisher exact test. OS was estimated by the Kaplan-Meier method. RS was computed by the ratio of the observed survival rate to the expected survival rate. The expected survival time of age- and gender-matched individuals was calculated from life tables of the general German population. Relative survival can be interpreted as survival from cancer after correction for other causes of death and therefore is used as an estimate for CSS. OS was also investigated with a Cox proportional hazards regression model. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented. The significance level was set at 5%.

2.4. Random samples

For fair comparisons of survival curves between LN-positive patients with or without RP, random samples were generated. The frequency distribution of the WHO grade and prostate-specific antigen (PSA) variables in the group without prostatectomy served as a reference to obtain five random samples from the group with prostatectomy. Survival curves of these samples are also presented.

3. Results

OS and RS rates for this population-based sample (n = 27 956) are presented in Fig. 1. The 5-yr OS was 76.7%

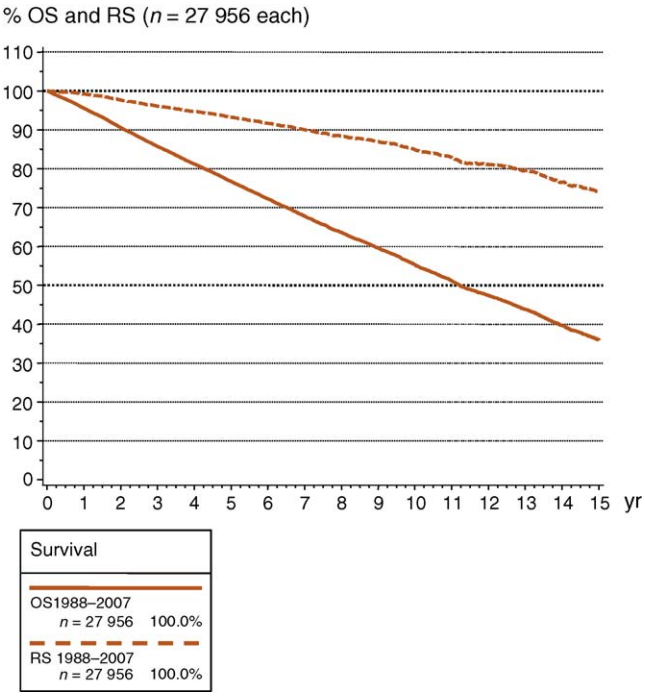

Fig. 1 – (a) Overall survival (OS) and (b) relative survival (RS).

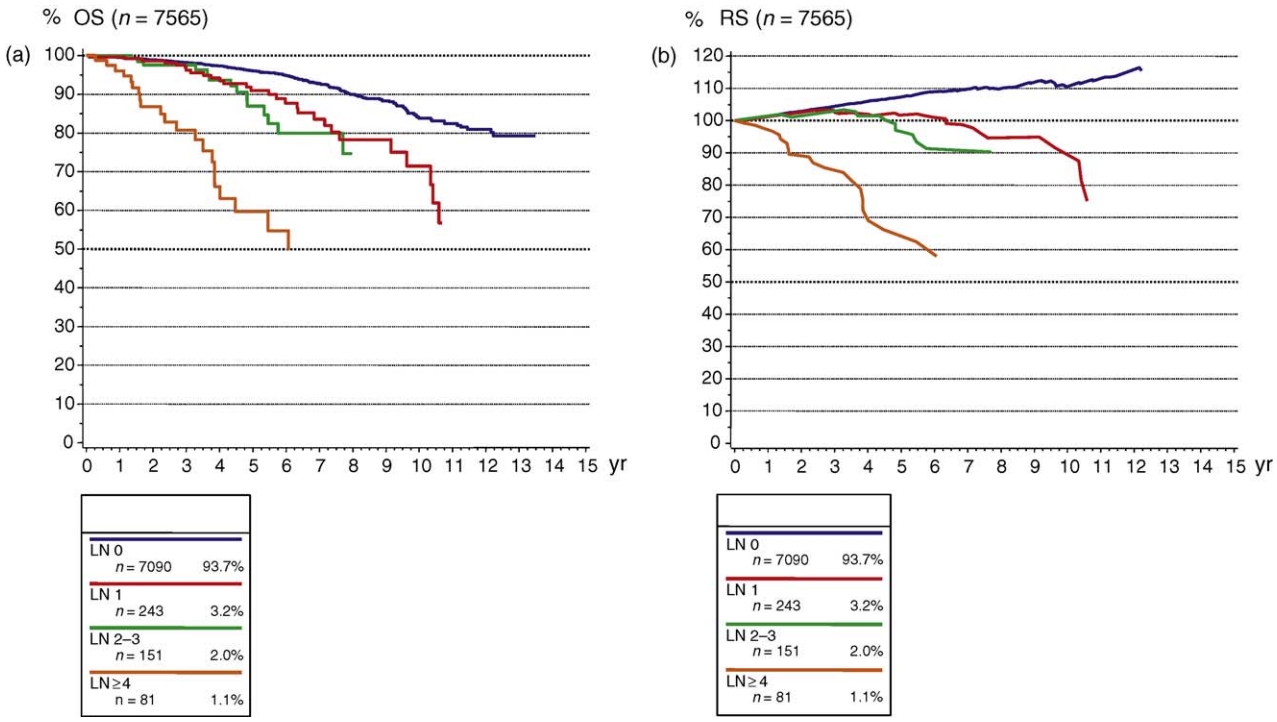

Fig. 2 – (a) Overall survival (OS) and (b) relative survival (RS) according to positive lymph nodes (LNs) after radical prostatectomy for all patients of the Munich Cancer Registry with detailed information of the exact number of positive LNs. RS is computed by the ratio of the observed survival rate to the expected survival rate of the general German population. Values of >100% describe a better prognosis relative to the general population.

(RS was 93.3%) and 10-yr OS was 55.2% (RS was 84.9%) in this cohort. Fig. 2 shows OS and RS for patients with PLND and complete prostatectomy, according to the number of positive LNs, and demonstrates the prognostic value of LN status.

Table 1 lists the clinical and pathologic characteristics for 1413 patients that composed the current study cohort. The median age was 65.4 yr. Patients with prostatectomy were slightly younger, had a better prognostic clinical T-stage distribution, comparable grade, and lower PSA values compared to patients without prostatectomy. In Table 2, all 938 patients with a positive LN status and available grade and PSA values are presented. Following PLND, 688 LN-positive patients underwent a completed prostatectomy and 250 did not. The frequency distribution of the grade and PSA variables in the group without prostatectomy served as a reference to obtain five random samples of the group with prostatectomy. Age as well as the (consequently identical) PSA and grade distributions for these five random samples are also shown in Table 2 ($n = 219$ in each group). Because each sample could be drawn from a large cohort, different patients were selected, as indicated by the varying age distributions. Fig. 3 depicts OS and RS for LN-positive patients with and without prostatectomy as well as for the five random samples. Differences in survival are impressive in favor of patients with completed prostatectomy: 5-yr OS for patients with prostatectomy was 83.7% (RS was 94.9%) and was 60.1% (RS was 70.5%) for patients without prostatectomy; the 10-yr OS was 63.8% (RS was 86.2%) and 28.2% (RS was 40.5%), respectively. The absolute differences of OS rates are 23.6% after 5 yr and 35.6% after 10 yr, and differences of RS rates are 24.4% and 45.7% for 5-yr and 10-yr follow-up, respectively.

Results of the Cox regression survival analysis are presented in Table 3. After adjustment for age, clinical T category, number of positive LNs, WHO grade, and PSA for LN-positive patients, a HR of 2.04 (95% CI, 1.59–2.63) resulted for patients with PLND and abandoned prostatectomy, indicating the benefit of prostatectomy, even in node-positive cases.

4. Discussion

Recent studies have demonstrated that RP is a valid option for patients with locally advanced disease [1,5,6]. RP was rarely performed before the 1980s and revolutionized the early 1980s when it was introduced as the accepted form of surgical treatment for localized prostate cancer [13–15]. When RP was first performed, surgery was commonly abandoned if suspicious pelvic LNs were detected during PLND; the patient was then considered to have systemic disease. This strategy was based on the idea that LN-positive patients would not have a survival benefit due to the surgical removal of the prostate. Specifically, an European Organization for Research and Treatment of Cancer (EORTC) study initiated in 1988 was based on this hypothesis and greatly influenced the protocol of some hospitals [7]. Recently, therapeutic approaches have changed, and urologists have started to experience good cancer-specific results in LN-positive prostate cancer patients [8–12]. Today, the surgical approach includes PLND and complete

Table 1 – Clinical characteristics for patients with positive lymph node status

Characteristics	Node-positive patients without prostatectomy *n* = 456	Node-positive patients with prostatectomy *n* = 957	Node-positive patients *n* = 1413
Period			
1988–1994, *n* (%)	159 (34.8)	281 (29.4)	440 (31.1)
1995–2001, *n* (%)	181 (39.7)	344 (36.0)	525 (37.2)
2001–2007, *n* (%)	116 (25.4)	332 (34.7)	448 (31.7)
Age			
Mean (median), yr	66.8 (66.5)	64.5 (65)	65.3 (65.4)
Age <60 yr, *n* (%)	92 (20.2)	230 (24.0)	322 (22.8)
Age 60–69 yr, *n* (%)	224 (49.2)	527 (55.1)	751 (53.2)
Age 70–74 yr, *n* (%)	71 (15.6)	159 (16.6)	230 (16.3)
Age ≥75 yr, *n* (%)	69 (15.1)	41 (2.3)	110 (7.8)
T category			
T1, *n* (%)	23 (5.5)	47 (6.3)	70 (6.0)
T2, *n* (%)	95 (22.7)	286 (38.0)	381 (32.6)
T3, *n* (%)	201 (48.1)	380 (50.5)	581 (49.8)
T4, *n* (%)	99 (23.7)	39 (5.2)	138 (11.8)
T missing values or TX[a], *n (%)*	*38 (8.3)*	*205(21.4)*	*243 (17.2)*
No. of positive LNs			
LN 1, *n* (%)	42 (34.4)	243 (51.3)	285 (47.8)
LN 2–3, *n* (%)	51 (41.8)	150 (31.7)	201 (33.7)
LN ≥4, *n* (%)	29 (23.8)	81 (17.1)	110 (18.5)
LN+ but number of positive LN not available[a], *n (%)*	*334 (73.3)*	*483 (50.5)*	*817 (57.8)*
Histopathologic grade			
G1, *n* (%)	13 (3.1)	12 (1.3)	25 (1.9)
G2, *n* (%)	191 (45.1)	434 (46.9)	625 (46.3)
G3/4, *n* (%)	220 (51.9)	479 (51.8)	699 (51.8)
Grading missing values or GX[a], *n (%)*	*32 (7.0)*	*32 (3.4)*	*64 (4.5)*
PSA			
<4 ng/ml, *n* (%)	12 (5.6)	32 (4.6)	44 (4.6)
4–10 ng/ml, *n* (%)	40 (15.2)	164 (23.4)	204 (21.2)
>10–20 ng/ml, *n* (%)	40 (15.2)	211 (30.1)	251 (26.0)
>20 ng/ml, *n* (%)	171 (65.0)	294 (41.9)	465 (48.2)
PSA missing values[a], *n* (%)	*193 (42.3)*	*256 (26.8)*	*449 (31.8)*
Adjuvant radiotherapy			
Radiotherapy: no, *n* (%)	349 (76.5)	773 (80.8)	1122 (79.4)
Radiotherapy: yes, *n* (%)	107 (23.5)	184 (19.2)	291 (20.6)
Adjuvant hormone therapy			
Hormone therapy: no, *n* (%)	88 (19.3)	267 (27.9)	355 (25.1)
Hormone therapy: yes, *n* (%)	368 (80.7)	690 (72.1)	1058 (74.9)
Follow-up			
Mean (median) follow-up for patients alive, yr	5.3 (5.)	6.7 (5.8)	6.4 (5.6)

LN = lymph node; PSA = prostate-specific antigen.
[a] The percentage of the subcategories is related to the sum of each item with available data; missing values are not taken into account.

RP, regardless of the intraoperative diagnosis of LN status. Interestingly, no large-scale population-based data are available to support the completion of RP in LN-positive cases. In the current analysis, the absolute differences in OS and RS are 23.6% and 35.6% after 5 yr and 10 yr, respectively, in patients undergoing PLND with or without RP; the differences in RS rates were 24.4% and 45.7% after 5 yr and 10 yr, respectively. These survival rates are nearly identical to reports in the literature [7,8,12]. These findings indicate that prostate cancer patients treated with complete RP may have improved survival compared to patients with abandoned RP. This obvious advantage should encourage urologists to complete RP, regardless of pelvic LN status.

In recent years, questions regarding the extent of PLND have been expressed. According to Bader et al [9], meticulous LN dissection "seems not only a staging procedure but may also have a possible positive impact on disease progression and long-term disease-free survival." Another study from the same institution with 122 patients revealed that prostate cancer-specific outcome in patients undergoing extended PLND significantly differed [10]. After 10 yr, patients with two or more positive nodes and patients with three or more positive nodes had a CSS of 78.6% and 33.4%, respectively; these findings are comparable with our results. The cut point of two or more positive LNs, however, cannot be reproduced with our data. It was also found that the diameter of an individual LN metastasis and its extranodal extension have a significant prognostic influence [16–18].

Today it is recognized that limited versus extended PLND is defined by the anatomical extent of PLND and not

Table 2 – Clinical characteristics for patients with positive lymph node status[a] and for five random samples

Characteristics	Node-positive patients without prostatectomy	Node-positive patients with prostatectomy	Node-positive patients with prostatectomy: Random sample 1 *n* = 219	Node-positive patients with prostatectomy: Random sample 2 *n* = 219	Node-positive patients with prostatectomy: Random sample 3 *n* = 219	Node-positive patients with prostatectomy: Random sample 4 *n* = 219	Node-positive patients with prostatectomy: Random sample 5 *n* = 219
	n = 938[a]						
	n = 250	*n* = 688					
Age							
Mean (median), yr	67.4 (67.2)	64.5 (64.8)	65.3 (65.7)	64.3 (64.9)	63.9 (64.3)	64.4 (64.3)	64.2 (64.6)
10th percentile, yr	57.7	56.2	56.8	55.4	55.1	56.3	55.3
90th percentile, yr	76.6	72.6	73.1	72.5	71.6	71.9	72.9
Age <60 yr, *n* (%)	42 (16.8)	166 (24.1)	44 (20.1)	49 (22.4)	48 (21.9)	51 (23.3)	52 (23.7)
Age 60–69 yr, *n* (%)	124 (49.6)	384 (55.8)	129 (58.9)	128 (58.5)	123 (56.2)	128 (58.5)	125 (57.1)
Age 70–74 yr, *n* (%)	47 (18.8)	111 (16.1)	37(16.9)	35 (16.0)	37 (16.9)	34 (15.5)	34 (15.5)
Age ≥75 yr, *n* (%)	37 (14.8)	27 (3.9)	9 (4.1)	7 (3.2)	11 (5.0)	6 (2.7)	8 (3.7)
T category							
T1, *n* (%)	18 (7.7)	38 (6.6)	14 (7.4)	11 (5.9)	12 (6.5)	13 (6.7)	12 (6.3)
T2, *n* (%)	63 (26.8)	241 (41.8)	72 (38.1)	77 (41.0)	69 (37.3)	81 (41.5)	79 (41.6)
T3, *n* (%)	105 (44.7)	275 (47.7)	93 (49.2)	91 (48.4)	97 (52.4)	92 (47.2)	92 (48.4)
T4, *n* (%)	49 (20.9)	23 (4.0)	10 (5.3)	9 (4.8)	7 (3.8)	9 (4.6)	7 (3.7)
T missing values or TX[b], *n* (%)	*15 (6.0)*	*111 (16.1)*	*30 (13.7)*	*31 (14.2)*	*34 (15.5)*	*24 (11.0)*	*29 (13.2)*
No. of positive LNs							
LN 1, *n* (%)	26 (27.9)	209 (50.7)	65 (52.4)	54 (43.6)	55 (44.4)	61 (50.0)	56 (45.5)
LN 2–3, *n* (%)	41 (44.1)	132 (32.0)	30 (24.2)	44 (35.5)	40 (32.3)	32 (26.2)	39 (31.7)
LN ≥4, *n* (%)	26 (28.0)	71 (17.2)	29 (23.4)	26 (21.0)	29 (23.4)	29 (23.8)	28 (22.8)
LN+ but no. of LN+ not available[b], *n* (%)	*157 (62.8)*	*276 (40.1)*	*95 (43.4)*	*95 (43.4)*	*95 (43.4)*	*97 (44.3)*	*96 (43.8)*
PSA and grade							
<4 ng/ml and G1/2, *n* (%)	7 (2.8)	11 (1.6)	6 (2.7)	6 (2.7)	6 (2.7)	6 (2.7)	6 (2.7)
<4 ng/ml and G3/4, *n* (%)	2 (0.8)	21 (3.1)	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)
4–10 ng/ml and G1/2, *n* (%)	19 (7.6)	69 (10.0)	17 (7.7)	17 (7.7)	17 (7.7)	17 (7.7)	17 (7.7)
4–10 ng/ml and G3/4, *n* (%)	19 (7.6)	94 (13.7)	17 (7.7)	17 (7.7)	17 (7.7)	17 (7.7)	17 (7.7)
>10–20 ng/ml and G1/2, *n* (%)	22 (8.8)	88 (12.8)	19 (8.7)	19 (8.7)	19 (8.7)	19 (8.7)	19 (8.7)
>10–20 ng/ml and G3/4, *n* (%)	16 (6.4)	117 (17.0)	14 (6.4)	14 (6.4)	14 (6.4)	14 (6.4)	14 (6.4)
> 20 ng/ml and G1/2, *n* (%)	71 (28.4)	142 (20.6)	62 (28.3)	62 (28.3)	62 (28.3)	62 (28.3)	62 (28.3)
> 20 ng/ml and G3/4, *n* (%)	94 (37.6)	146 (21.2)	82 (37.4)	82 (37.4)	82 (37.4)	82 (37.4)	82 (37.4)

LN = lymph node; PSA = prostate-specific antigen.

[a]For 938 of 1413 N+ patients for whom grade and PSA were completely available.

[b]The percentage of the subcategories is related to the sum of each item with available data; missing values are not taken into account.

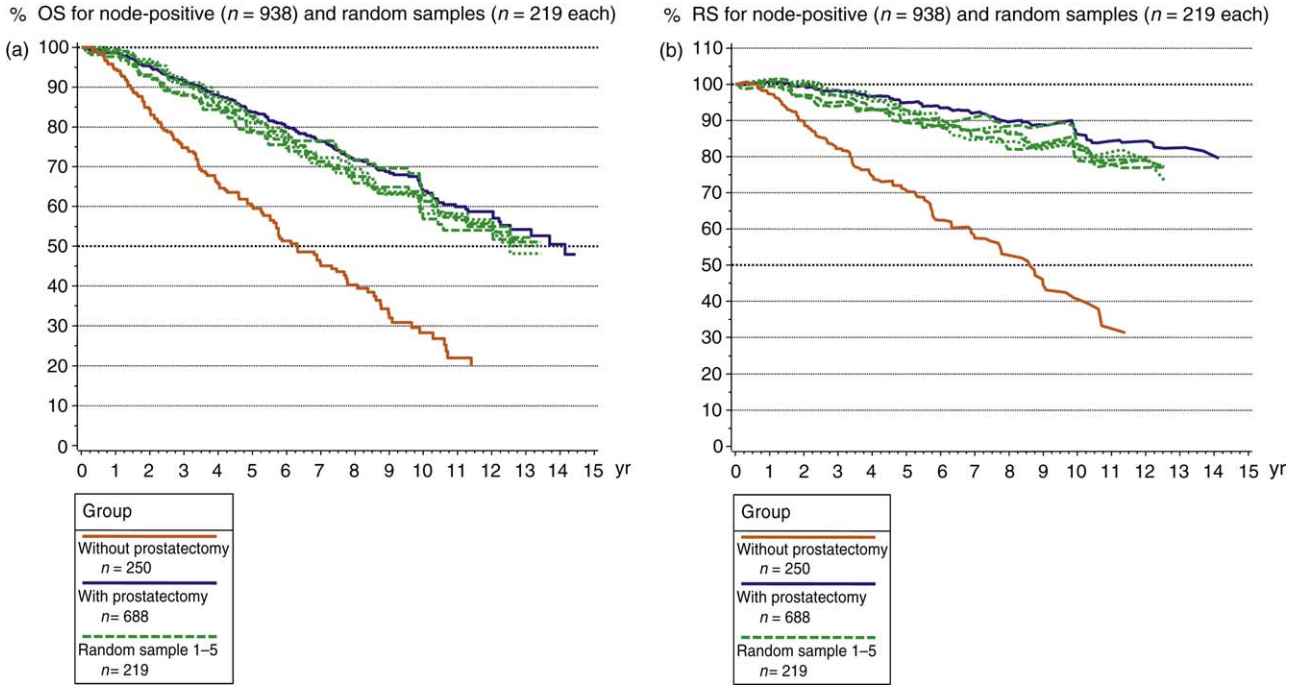

Fig. 3 – (a) Overall survival (OS) and (b) relative survival (RS) for patients with positive lymph node status according to radical prostatectomy and for five random samples of the cohort with prostatectomy.

imperatively by the number of LNs removed [19]. Furthermore, it is suggested that if PLND is indicated, it should be performed as an extended PLND [20,21]. We are unaware of the form of PLND that was performed in our study. In the future, prospective trials on the extent of LN dissection should clarify this important aspect of prostate cancer research.

Because a growing number of randomized studies of other cancers also have found no survival advantage in LN dissection cohorts, the question of whether to abandon any lymphadenectomy in prostate cancer should be evaluated [22]. This approach does not contradict the fact that the number of positive LNs is a prognostic factor. Positive LNs are a good survival indicator but probably are not the cause of metastases. Although this prediction is hypothetical, it seems generalizable because pathways of dissemination to organ-specific colonization of solid tumors seem comparable [23].

Several points of our study warrant further discussion. First and foremost, the analyzed data were generated over a long period of time with an unknown number of surgeons. An advantage of the MCR data is that they represent "real life" and therefore are not affected by a small number of subspecialized surgeons. Even though the data are collected prospectively, the analysis is retrospective. This approach has many limitations, such as a lack of randomization and, consequently, an incomplete or absent account of measured or unmeasured confounders. Nevertheless, the multivariate adjustment reduces this weakness in the study design.

Second, survival does not depend on LN status alone but also on pathologic characteristics such as local tumor extent. The high incidence of non–organ-confined cancers in our series of positive LNs, for example, is a confounding factor. This finding is in line with work by Schumacher et al [10,24] but has not been described by other studies.

Third, according to our knowledge, most patients without RP received adjuvant hormonal treatment. This treatment can be criticized and considered a confounder, but it represents common urologic practice. According to the only randomized trial by Messing et al [25], early hormone therapy benefits patients with nodal metastases who received prostatectomy compared with those who received deferred treatment. Many patients, however, have not only node-positive prostate cancer but also non–organ-confined prostate cancer. The trend of an advantage of early hormonal therapy in patients without local treatment is suggested by the data from the EORTC 30486 study [7]. Schroder et al found a 23% nonsignificant trend in favor of early hormonal versus delayed treatment. The trial, however, was underpowered to show equivalence or superiority. Interestingly, other studies were not able to support the hypothesized benefit of early hormonal therapy [24,26,27]. Keeping in mind that prognosis depends on the number of positive nodes and the extent and size of the metastasis, one could argue that early hormonal therapy may constitute overtreatment [10,16–18,28]. A short postoperative PSA doubling time was reported as a negative prognostic factor and thus may serve to categorize patients into different groups for adjuvant treatment regimens [29].

Another interesting aspect of adjuvant therapy was alluded to by da Pozzo et al [30]. This group was the first to investigate the role of hormonal therapy with or without RT in node-positive patients. They found a significant protective role for adjuvant hormonal therapy and RT in CSS of node-positive patients [30]. Unfortunately, there are no

Table 3 – Cox proportional hazards analysis of overall duration of survival for patients with positive lymph node status

Patients: n = 938 Events: n = 295 Covariates	HR	95% CI	p
Age	1		0.0002*
<60 yr	1.053	Reference	
60–69 yr	1.285	0.77–1.44	
70–74 yr	2.477	0.89–1.86	
≥75 yr		1.58–3.89	
T category			<0.0001*
cT1	1	Reference	
cT2	1.598	0.77–3.34	
cT3	1.850	0.90–3.81	
cT4	4.202	1.95–9.03	
cT not available	1.828	0.80–4.21	
No. of positive LNs			0.0006*
LN 1	1	Reference	
LN 2–3	0.979	0.56–1.73	
LN ≥4	2.461	1.46–4.16	
LN+, exact no. of positive LNs not available	1.737	1.15–2.63	
Histopathologic grade			<0.0001
G1/2	1	Reference	
G3/4	1.650	1.30–2.09	
PSA			0.0327*
<4 ng/ml	1	Reference	
4–10 ng/ml	1.061	0.55–2.06	
>10–20 ng/ml	0.675	0.35–1.31	
>20 ng/ml	1.091	0.59–2.03	
Surgery			<0.0001
Prostatectomy: yes	1	Reference	
Prostatectomy: no	2.042	1.59–2.63	

CI = confidence interval; HR = hazard ratio; LN = lymph node; PSA = prostate-specific antigen.
* Global test.

data from a randomized trial in patients with positive nodes and abandoned RP receiving adjuvant therapy.

Finally, our study spans >20 yr and the data in the present analysis may not represent current practice patterns, considering the fact that diagnostic tests, surgical techniques, and follow-up protocols might have changed over time. Furthermore, our analyses could not incorporate all parameters that one would like. To really shed light on the topic, one would have to perform a randomized trial, which we realize is almost impossible to achieve.

5. Conclusions

Our long-term investigation of node-positive prostate cancer patients treated with PLND and completed or abandoned RP shows significantly improved survival in patients with completed RP. These results suggest that intraoperative frozen section analysis with abandonment of RP may not be justified.

Author contributions: Jutta Engel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Engel, Hölzel.
Acquisition of data: Baur, Beer, Chaussy, Geschwend, Oberneder, Rothenberger, Stief.
Analysis and interpretation of data: Engel, Bastian, Hölzel.
Drafting of the manuscript: Engel, Bastian, Hölzel.
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References

[1] Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. Eur Urol 2008;53:68–80.
[2] Dahm P, Yeung LL, Chang SS, Cookson MS. A critical review of clinical practice guidelines for the management of clinically localized prostate cancer. J Urol 2008;180:451–9, discussion 460.
[3] Walz J, Gallina A, Saad F, et al. A nomogram predicting 10-year life expectancy in candidates for radical prostatectomy or radiotherapy for prostate cancer. J Clin Oncol 2007;25:3576–81.
[4] Walsh PC, DeWeese TL, Eisenberger MA. Clinical practice. Localized prostate cancer. N Engl J Med 2007;357:2696–705.
[5] Hsu C-Y, Joniau S, Oyen R, Roskams T, Van Poppel H. Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. Eur Urol 2007;51:121–9, discussion 128–9.
[6] Freedland SJ, Partin AW, Humphreys EB, Mangold LA, Walsh PC. Radical prostatectomy for clinical stage T3a disease. Cancer 2007;109:1273–8.
[7] Schroder FH, Kurth KH, Fossa SD, et al. Early versus delayed endocrine treatment of pN1-3 M0 prostate cancer without local treatment of the primary tumor: results of European Organisation for the Research and Treatment of Cancer 30846—a phase III study. J Urol 2004;172:923–7.
[8] Cheng L, Zincke H, Blute ML, Bergstralh EJ, Scherer B, Bostwick DG. Risk of prostate carcinoma death in patients with lymph node metastasis. Cancer 2001;91:66–73.
[9] Bader P, Burkhard FC, Markwalder R, Studer UE. Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure?. J Urol 2003;169:849–54.
[10] Schumacher MC, Burkhard FC, Thalmann GN, Fleischmann A, Studer UE. Good outcome for patients with few lymph node metastases after radical retropubic prostatectomy. Eur Urol 2008;54:344–52.

[11] Briganti A, Capitanio U, Chun FK-H, et al. Impact of surgical volume on the rate of lymph node metastases in patients undergoing radical prostatectomy and extended pelvic lymph node dissection for clinically localized prostate cancer. Eur Urol 2008;54:794–804.
[12] Daneshmand S, Quek ML, Stein JP, et al. Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. J Urol 2004;172:2252–5.
[13] Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. Prostate 1983;4:473–85.
[14] Walsh PC, Mostwin JL. Radical prostatectomy and cystoprostatectomy with preservation of potency. Results using a new nerve-sparing technique. Br J Urol 1984;56:694–7.
[15] Heidenreich A. Radical prostatectomy in 2007: oncologic control and preservation of functional integrity. Eur Urol 2008;53:877–9.
[16] Fleischmann A, Schobinger S, Markwalder R, et al. Prognostic factors in lymph node metastases of prostatic cancer patients: the size of the metastases but not extranodal extension independently predicts survival. Histopathology 2008;53:468–75.
[17] Fleischmann A, Schobinger S, Schumacher M, Thalmann GN, Studer UE. Survival in surgically treated, nodal positive prostate cancer patients is predicted by histopathological characteristics of the primary tumor and its lymph node metastases. Prostate 2009;69: 352–62.
[18] Boormans JL, Wildhagen MF, Bangma CH, Verhagen PC, van Leenders GJ. Histopathological characteristics of lymph node metastases predict cancer-specific survival in node-positive prostate cancer. BJU Int 2008;102:1589–93.
[19] Heidenreich A, Ohlmann CH, Polyakov S. Anatomical extent of pelvic lymphadenectomy in patients undergoing radical prostatectomy. Eur Urol 2007;52:29–37.
[20] Briganti A, Blute ML, Eastham JH, et al. Pelvic lymph node dissection in prostate cancer. Eur Urol 2009;55:1251–65.
[21] Schlomm T, Borgermann C, Heinzer H, Rubben H, Huland H, Graefen M. Role of lymph node dissection in prostate cancer [in German]. Urologe A 2009;48:37–45.
[22] Gervasoni Jr JE, Sbayi S, Cady B. Role of lymphadenectomy in surgical treatment of solid tumors: an update on the clinical data. Ann Surg Oncol 2007;14:2443–62.
[23] Nguyen DX, Bos PD, Massague J. Metastasis: from dissemination to organ-specific colonization. Nat Rev Cancer 2009;9:274–84.
[24] Boorjian SA, Thompson RH, Siddiqui S, et al. Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. J Urol 2007;178:864–70, discussion 870–1.
[25] Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006;7:472–9.
[26] Frohmuller HGW, Theiss M, Manseck A, Wirth MP. Survival and quality of life of patients with stage D1 (T1-3 pN1-2 M0) prostate cancer: radical prostatectomy plus androgen deprivation versus androgen deprivation alone. Eur Urol 1995;27: 202–6.
[27] Wong YN, Freedland S, Egleston B, Hudes G, Schwartz JS, Armstrong K. Role of androgen deprivation therapy for node-positive prostate cancer. J Clin Oncol 2009;27:100–5.
[28] Briganti A, Karnes JR, Da Pozzo LF, et al. Two positive nodes represent a significant cut-off value for cancer-specific survival in patients with node-positive prostate cancer. A new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. Eur Urol 2009;55: 261–70.
[29] Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005;294:433–9.
[30] Da Pozzo LF, Cozzarini C, Briganti A, et al. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. Eur Urol 2009;55: 1003–11.