Phase 3 Study of Adjuvant Radiotherapy Versus Wait and See in pT3 Prostate Cancer: Impact of Pathology Review on Analysis

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Abstract

Background: In a randomised trial, radical prostatectomy (RP) followed by adjuvant radiotherapy (aRT) was compared with RP alone in patients with pT3 pN0 prostate cancer with or without positive margin at local pathology (German Cancer Society trial numbers ARO 96-02/AUO AP 09/95).

Objective: A pathology review was performed on 85\% of RP specimens of patients to investigate the influence of pathology review on the analysis.

Design, setting, and participants: Patients post-RP (n = 385) were randomised before achieving an undetectable prostate-specific antigen (PSA) level to either wait and see (n = 192) or 60 Gy aRT (n = 193). Of 307 patients with undetectable PSA after RP, 262 had pathology review. These results were included prospectively into the analysis.

Outcome measurements and statistical analysis: Agreement between local and review pathology was measured by the total percentage of agreement and by simple kappa statistics. The prognostic reliability for the different parameters was analysed by Cox regression model. Event-free rates were determined by Kaplan-Meier analysis with a median follow-up of 40 mo for the wait-and-see arm and 38.5 mo for the aRT arm.

Results and limitations: There was fair concordance between pathology review and local pathologists for seminal vesicle invasion (pT3c: 91\%; k = 0.76), surgical margin status (84\%; k = 0.65), and for extraprostatic extension (pT3a/b: 75\%; k = 0.74). Agreement was much less for Gleason score (47\%; k = 0.42), whereby the review pathology resulted in a shift to Gleason score 7. In contrast to the analysis of progression-free survival with local pathology, the multivariate analysis including review pathology revealed PSMs and Gleason score >6 as significant prognostic factors.

Conclusions: Phase 3 studies of postoperative treatment of prostate cancer should be accomplished in the future with a pathology review. In daily practice, a second opinion by a pathologist experienced in urogenital pathology would be desirable, in particular, for high-risk patients after RP.

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1. Introduction

For patients with pT3 prostate cancer (PCa) and/or positive surgical margins (PSMs), two options can be offered after radical prostatectomy (RP): either immediate radiotherapy to the surgical bed or clinical and biologic monitoring followed by salvage radiotherapy, ideally when the prostate-specific antigen (PSA) level rises but does not exceed 0.5 ng/ml [1–3].

Until now, three randomised trials demonstrated a nearly 20% absolute benefit for biochemical progression-free survival (BPFS) after adjuvant radiation therapy (aRT) compared with a wait-and-see policy (W+S) for patients with pT3 R1 or R0 PCa after RP [4–6].

The most recent of these randomised, multicentre, phase 3 trials was initiated in 1996 by the Arbeitsgemeinschaft Radiologische Onkologie (ARO) and Urologische Onkologie (AUO) (Working Group Radiologic Oncology and Urologic Oncology) of the German Cancer Society to test the hypothesis that immediate radiation therapy (RT) after RP improves BPFS in patients with pT3 tumours with or without PSMs at local pathology and undetectable PSA [6].

To enable accurate pathologic staging, the RP specimen should be processed uniformly. Several consensus guidelines were published recently [7,8]. The impact of pathology review on the results of randomised studies of the primary treatment of PCa is well known. The Radiation Therapy Oncology Group trial 8531 randomised patients with locally advanced PCa to either androgen suppression therapy (AST) or no AST after the administration of RT. In a subgroup of patients with pathologically reviewed biopsy specimens with Gleason score 8–10, there was a significant difference in overall survival [9]. However, comparable information is scarce concerning the postoperative treatment of PCa. The only published results come from one clinical trial with data from 50% of the patients who were retrospectively analysed [10,11].

Thanks to two pathologists experienced in urogenital pathology, we performed a prospective pathology review on 85% of RP specimens from patients participating in the ARO/AUO trial before starting the analysis. The aim of our study was to investigate the influence of pathology review on the analysis.

2. Materials and methods

2.1. Patients and surgical specimens

From April 1997 to September 2004, 385 patients from 22 institutions were randomised before achieving an undetectable PSA levels to either aRT with 60 Gy (n = 193) or a W+S policy (n = 192). Inclusion criteria were histologically proven adenocarcinoma of the prostate with no known distant metastases and a stage pT3–pT4 pN0 with PSMs or negative surgical margins at local pathology. Tumour stage was determined according to the 1992 Union Internationale Contre le Cancer (UICC) classification [12]. Seventy-eight patients did not achieve an undetectable PSA level after RP. The present analysis focuses on the remaining 307 patients with undetectable PSA level after RP. The protocol was approved by the local ethics review committee of each participating centre. Written informed consent was obtained from all patients. The results of the analysis without the comparison between local and review pathology were published previously [6].

2.2. Pathologic review

The local pathologists used individual protocols, but the pathology review was standardised per protocol. After formalin fixation, the surgical specimen was marked with ink over the entire resection margin. Then the prostate was sectioned from the distal margins to the bladder neck.

The evaluation comprised grading according to the original Gleason score system [13] and staging according to UICC guidelines from 1992 because these allowed a better stratification of tumour extension in stage pT3. Furthermore, localisation, sidedness, and length of PSMs in millimetres (stratified by nine different localisations: apex, anterior, lateral right and left (R/L), dorsal R/L, neurovascular bundle R/L, and base) were registered. A PSM was recorded if tumour glands unequivocally reached an inked margin or margin with cauterisation artefacts, in which the glands could be identified unequivocally. In the identical topography, extraprostatic extension (EPE) was recorded. EPE was defined as extension of carcinomatous glands in contact with adipose tissue, in the niveau of immediate adjacent adipose tissue, or leaving the smooth contour of the prostate in the region of neurovascular bundle R/L. The diagnosis of bladder-neck infiltration was made if large, smooth, contoured bundles typical of detrusor muscle were infiltrated by atypical glands and normal prostate glands were not present. Seminal vesicle invasion was registered if at least the smooth-muscle wall of these glands was infiltrated. Clinical course of the patients, including pre- and postoperative PSA values, were not known to the reviewing pathologist at the time of histologic evaluation.

A total of 262 prostatectomy specimens provided by local pathologists of 22 centres were reviewed. The remaining 38 cases were not evaluable because either only a small amount of paraffin-embedded tissue (one to four blocks) was available, or the report of the local pathologist was missing, and/or the precise localisation of the tissue blocks was unknown (eg, which side). In 65% of cases, the original slides and paraffin-embedded tissue were sent for pathology review, and in 35% of cases, only blocks were reviewed. Additionally, residual formalin-fixed tissue was available in 16% of cases. This was embedded completely by the reference pathology. Regional lymph nodes were additionally available in 43% of the cases. For 28% of cases, the specimens were embedded totally by the local pathologist; >90% of the prostate specimens were available for 22% of cases, 50–90% were available for 40%, and 20–50% were available for 10%. The completeness of embedding was estimated using the weight of the specimen, the number of paraffin-embedded tissue blocks, and the original report from the local pathologist. The procedure of embedding the specimen by the local pathologist was not uniform. The reviewing pathologists had access to the original reviews.

From each paraffin block, a haematoxylin-eosin stained slide was prepared. In 18% of the cases, whole-mount sections could be evaluated. The pathology review of all specimens was done together by two pathologists experienced in urogenital pathology (R.G., S.S.)

2.3. Follow-up and end point

Details of the follow-up of the trial were described elsewhere. The overall median follow-up period for the analyses was 53.7 mo [6]. The main focus of the present work—the comparison between local and review pathology—was not updated, resulting in a median follow-up of 40 mo for the W+S arm and 38.5 mo for the aRT arm.

The primary end point of the study was progression-free survival (PFS), with biochemical progression defined as two consecutive PSA...
increases above the detection limit of the respective PSA assay, local or distant clinical recurrence, or death for any reason, whichever occurred first.

2.4. Statistics

Two analyses were performed, the first solely based on local pathology and the second including pathology review (n = 262 patients; 85%). The remaining 38 patients were categorised according to local pathology in the second analysis with the local pathology (Table 1).

Agreement between local and review pathology was measured by the total percentage of agreement and by simple kappa statistics [14]. The impact of local and review pathology on the prognostic reliability was analysed by Cox regression model, estimating the hazard ratios (HRs) and 95% confidence intervals (CIs). Event-free rates were determined by Kaplan-Meier analysis [15].

3. Results

Median follow-up was 40 mo for the W+S group and 38.5 mo for the aRT group. The BPFS at 4 yr increased to 81% for aRT compared with 60% for W+S (HR: 0.4; \( p < 0.0001 \)). In the first analysis including subgroup analysis (local pathology only), patients with a preoperative PSA level > 10 ng/ml and tumour stage \( pT3b \) profited significantly from aRT.

3.1. Level of agreement between review and local pathology

There was good concordance between review pathology and local pathologists regarding seminal vesicle invasion (\( pT3c \): 91%; \( \kappa = 0.76 \)), surgical margin status (84%; \( \kappa = 0.65 \)), and for EPE (\( pT3a/b \): 75%; \( \kappa = 0.74 \)) (Table 2).

PSMs increased to 69.4% (pathologic review: 231 of 333 specimens) compared with 62.5% (local pathologists: 208 of 333). Negative margins, as judged by local pathology, were scored positive in 30.4% of cases (38 of 125) and, conversely, 7.2% of the cases scored positive by local pathology (15 of 208) were judged negative by the pathology review.

Agreement was much less for Gleason score (47%; \( \kappa = 0.42 \)), whereby the pathology review resulted in a shift of the score from lower as well as higher levels to Gleason 7 (Table 2).

3.2. Influence of review pathology on prognostic impact of staging parameters

Consequently, and in contrast to the first analysis, in the second analysis including pathology review (38 patients without pathology review were categorised according to local pathology), patients with PSMs and a Gleason score > 6 profited significantly from radiotherapy (Table 3) (also in the multivariate analysis).

The multivariate analysis of PFS revealed Gleason score > 6, \( pT \) stage \( \geq pT3b \), PSMs, preoperative PSA level > 10 ng/ml, and radiotherapy as significant prognostic factors. Notably, PSMs and Gleason score > 6 were not significant in the analysis without review pathology (Table 3).

Patients with PSMs showed a trend toward a worse prognosis for PFS in the total group (with and without aRT) in the analysis with pathologic review (Fig. 1).

In the univariate analysis of the subgroup of patients with PSMs, aRT remained significant (Fig. 2). In the multivariate analysis, aRT and Gleason score were associated with significantly better prognosis.

Table 1 – The number of patients in different analysis steps

<table>
<thead>
<tr>
<th>Patients randomized</th>
<th>Patients with pathologic review, no. (%)</th>
<th>Patients excluded per protocol (detectable PSA level), no.</th>
<th>Included patients with undetectable PSA level, no.</th>
<th>Patients with pathologic review, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>385</td>
<td>336 (87)</td>
<td>78</td>
<td>307</td>
<td>262/307 (85)</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen.

Table 2 – Comparison between review and local pathology: surgical margins, \( pT \)-stage, and Gleason score

<table>
<thead>
<tr>
<th>Surgical margins</th>
<th>Local pathology, no. (%)</th>
<th>Review pathology, no. (%)</th>
<th>Concordance, % (( \kappa ) value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>208 (62.5)</td>
<td>231 (69.4)</td>
<td>84 (0.65)</td>
</tr>
<tr>
<td>Negative</td>
<td>125 (37.5)</td>
<td>102 (30.6)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Local pathology</th>
<th>Review pathology</th>
<th>Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>( &lt;7 )</td>
<td>139 (42.2)</td>
<td>106 (32.2)</td>
<td>47 (0.42)</td>
</tr>
<tr>
<td>7</td>
<td>109 (33.1)</td>
<td>181 (55.0)</td>
<td></td>
</tr>
<tr>
<td>( &gt;7 )</td>
<td>81 (24.6)</td>
<td>42 (12.8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>( pT )-stage</th>
<th>Local pathology</th>
<th>Review pathology</th>
<th>Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>( &lt;pT3a )</td>
<td>1 (0.3)</td>
<td>7 (2.1)</td>
<td>75 (0.74)</td>
</tr>
<tr>
<td>( pT3a )</td>
<td>171 (51.2)</td>
<td>141 (42.2)</td>
<td></td>
</tr>
<tr>
<td>( pT3b )</td>
<td>47 (14.1)</td>
<td>58 (17.4)</td>
<td></td>
</tr>
<tr>
<td>( pT3c )</td>
<td>114 (34.1)</td>
<td>97 (29.0)</td>
<td>91 (0.76)</td>
</tr>
<tr>
<td>( pT4 )</td>
<td>1 (0.3)</td>
<td>31 (9.3)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3 – Multivariate analysis, without and with review pathology, of progression-free intervals with therapy arm

<table>
<thead>
<tr>
<th>Factor</th>
<th>Statistical parameter</th>
<th>Without pathology review (n = 297)</th>
<th>With pathology review (n = 297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr ≥65</td>
<td>Relative risk</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>CI</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gleason score* ≥6</td>
<td>Relative risk</td>
<td>–</td>
<td>1.88</td>
</tr>
<tr>
<td></td>
<td>CI</td>
<td>–</td>
<td>1.15–3.08</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>&gt;0.05</td>
<td>0.012</td>
</tr>
<tr>
<td>pT stage ≥pT3b</td>
<td>Relative risk</td>
<td>2.32</td>
<td>2.08</td>
</tr>
<tr>
<td></td>
<td>CI</td>
<td>1.49–3.61</td>
<td>1.31–3.31</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>&gt;0.05</td>
<td>0.0019</td>
</tr>
<tr>
<td>Surgical margin status</td>
<td>Relative risk</td>
<td>–</td>
<td>1.67</td>
</tr>
<tr>
<td>Positive</td>
<td>CI</td>
<td>&gt;0.05</td>
<td>1.02–2.71</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>&gt;0.05</td>
<td>0.041</td>
</tr>
<tr>
<td>Preoperative PSA level, ng/ml &gt;10</td>
<td>Relative risk</td>
<td>1.78</td>
<td>1.72</td>
</tr>
<tr>
<td></td>
<td>CI</td>
<td>1.15–2.77</td>
<td>1.10–2.68</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.010</td>
<td>0.017</td>
</tr>
<tr>
<td>Therapy arm Radiotherapy</td>
<td>Relative risk</td>
<td>0.46</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>CI</td>
<td>0.29–0.73</td>
<td>0.29–0.72</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.00098</td>
<td>0.00086</td>
</tr>
</tbody>
</table>

CI = confidence interval; PSA = prostate-specific antigen.
*Gleason score and surgical margin status were statistically significant only after pathology review.

Fig. 1 – Progression-free survival (PFS) by surgical margins for all patients (n = 299): univariate analysis (a) without review pathology and (b) with review pathology. HR = hazard ratio; CI = confidence interval.

Fig. 2 – Kaplan-Meier plot of progression-free survival (PFS) (subgroup: positive surgical margins, pT3R1): univariate analysis (a) without review pathology (n = 175) and (b) with review pathology (n = 170). HR = hazard ratio; CI = confidence interval.
4. Discussion

The precise histologic assessment of RP specimens in patients with PCa is of major importance for an accurate risk assessment of disease recurrence. The three histopathologic parameters of greatest prognostic importance are pathologic stage, Gleason score, and surgical margin status, where pathologic stage includes assessment for seminal vesicle invasion and EPE. Several studies have previously assessed interobserver variability between the local pathologists and review pathologists in Gleason score in both the settings of needle biopsy and RP specimens [16–20]. In contrast, only five studies have evaluated interobserver variability in pathologic staging and margin status after RP [10,21–24]. It is well known that pathology review has a significant impact on the results of randomised studies of definitive treatment of PCa [9]. The situation is not as clear for postoperative treatment [10,11].

Major interobserver variations have been known from retrospective analyses. During the reexamination and reevaluation of prostatectomy specimens of 114 patients, Ekici et al. [21] found that Gleason grade and pathologic stage differed from the original statements in 32% and 24%, respectively. Also, significant discrepancies involved surgical margin status and EPE [21]. In the European Organisation for Research and Treatment of Cancer (EORTC) trial 22911, 552 RP specimens (from approximately 50% of the patients) were retrospectively reviewed by pathologists with experience in urogenital pathology, who examined all slides of the sample series [10]. Pathologic stage and surgical margin status were recorded. While there was close concordance between local and review pathology regarding seminal vesicle invasion (94%), less agreement was reached for EPE (58%) and for surgical margin status (69%). An agreement rate cannot be given for the Gleason score, because this was not determined by the local pathologists in the EORTC trial, but only in the retrospective analysis by van der Kwast et al. [10].

Up to now, the impact of pathology review has not been evaluated prospectively, although pathology data (e.g., margin status) influence the clinical course: Focal or extensive positive margins go along with a decreased disease-free survival (DFS). For instance, in patients with otherwise organ-confined disease, focal positive margins significantly decreased DFS [25]. Thus, the fact that 20% more PSMs were diagnosed by review pathology in our study is of particular importance.

Most likely, the discrepancies can be attributed to differences in the interpretation of the findings and/or overlooking of some pathology details related to the investigated parameters. As for surgical margins, during review, we strictly adhered to the rule that tumour cells should be in direct contact with ink to consider the margin positive, rather than distance to the inked surface. This is in line with the finding of Epstein et al. [26] that a close margin (i.e., <0.1 mm) should not be designated as PSM because it does not affect the prognosis. Also, lacerations in the capsule were accounted for, which can cause a false-positive margin diagnosis if tumour cells are covered by ink at these sites, due to leakage. Similarly, the presence of tumour cells on the outer surface of a specimen not covered by ink was not considered as evidence of a positive margin. According to current guidelines, margins were only considered positive if covered by ink (applied before sectioning of the RP specimen). Observing these rules during our review led to the emergence of surgical margin status as a prognostic parameter, which was maintained after inclusion of the (reviewed) Gleason score in the multivariate analysis.

A further potential source for discrepancies concerning the surgical margin status may be the assumption that the mere presence of carcinoma in sections of the apex would automatically signify a positive resection margin. This view dates back to when, in some institutions, the apex was cut in a transverse plane, precluding a proper evaluation of its resection margins.

Similar to published results [11,21], the level of agreement on seminal vesicle invasion was high. Apparently, most pathologists are aware of the requirement of tumour invasion of the muscular coat of the seminal vesicle. The Gleason-score agreement rate of only 47% found in our study is within the 36–73% range cited by previous studies [16,17,24].

Our 75% rate of agreement between review pathologists and local pathologists in evaluating EPE is virtually identical to the 69–70% rate found by van der Kwast et al. [10] and Netto et al. [24].

In our study, pathology review of RP specimens had a high impact on the prognostic-factor evaluation in multivariate analysis. In contrast to local pathology, two additional, independent risk factors were identified. The most important factor is the PSM. Our prospective results agree with the retrospective data of van der Kwast et al.: Regarding the status of the surgical margins, the prognostic value of the review assessment was stronger than the local assessment [10,11].

A potential limitation of our study may be that only cases with pathologic stage T3 with or without positive margin status (at local pathology) were included. However, the analysis of the EORTC trial included patients with pT2 R1 tumours. The effects of the pathology review were the same in this subgroup. Both studies indicate that the marked interobserver differences regarding tumour extension bear consequences for the outcome of trials on large groups of patients.

Another limitation may be the 38 patients without pathology review who were categorised according to local pathology in the second analyses. These patients were not excluded from the analyses for better comparability to the results of the main clinical-outcome publication [6].

5. Conclusions

In conclusion, and in prospective accordance with the retrospective data of van der Kwast et al. [10,11], future postoperative phase 3 studies of PCa should always include pathology review.

In daily practice, a second opinion by a pathologist experienced in urogenital pathology would be desirable,
particularly for high-risk patients after RP, when there is a conflicting discussion about aRT.

Author contributions: Dirk Bottke 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.


Drafting of the manuscript: Bottke, Wiegel. Critical revision of the manuscript for important intellectual content: Golz, Störlkel, Hinke, Siegmann, Hertle, Miller, Hinkelbein, Hinke, Bottke. Statistical analysis: None. Obtaining funding: Siegmann, Bottke, Hinke. Administrative, technical, or material support: Wiegel, Miller, Hinkelbein. Supervision: None. Other (specify): None.

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