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Review – Prostate Cancer

Adjuvant Radiotherapy for Patients with Locally Advanced Prostate Cancer—A New Standard?

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Abstract

Context: After radical prostatectomy (RPE) pathologically advanced disease is detected in 38% to 52% of patients. Retrospective data on the role of postoperative radiotherapy (RT) are controversial.
Objectives: To clarify in how far an adjuvant radiation treatment (ART) in cases of locally advanced disease affects outcome, three randomised trials have been started. The available data are critically reviewed.
Evidence acquisition: Relevant publications were detected by searching the Medical Literature Analysis and Retrieval System Online (MEDLINE) and the Public/Publisher MEDLINE (PUBMED; National Library of Medicine journal articles database) databases using the medical subject headings ''prostatic neoplasms,'' ''radiotherapy,'' and ''adjuvant.'' A major emphasis was placed on the results of the randomised trials.
Evidence synthesis: The European Organization for Research and Treatment of Cancer (EORTC) trial number 22911, Southwest Oncology Group (SWOG) trial number 8794, and German Intergroup trial ARO 96-02/AUO AP 09/95 randomised patients to receive ART with 60 Gray (Gy) and 60–64 Gy (SWOG trial), respectively. The majority of patients had undetectable PSA levels postoperatively. The data concordantly show that ART improves biochemical progression-free survival rates (EORTC trial, progression-free survival rate after 5 yr: 74.0% with ART vs 52.6% without ART; SWOG trial, after 5 yr: ~73% vs ~44%, respectively; and ARO 96-02/AUO AP 09/95 trial, after 5 yr: 72% vs 54%, respectively). The EORTC trial shows improved local control of cancer progression ($p < 0.0001$) for treated patients. The SWOG trial demonstrates an improved freedom from hormonal treatment (5-yr: 21% with ART vs 10% without ART). A statistically significant benefit with regard to metastasis-free survival and overall survival was not seen. Genitourinary and gastrointestinal toxicity was moderate, with late side-effects (≥ grade 3) between 3% (in the ARO 96-02 trial) and <5% (in the EORTC trial).
Conclusion: Biochemical progression-free survival and local control are significantly improved by postoperative RT with 60 Gy. Patients should be offered adjuvant treatment when they are at high risk for local relapse (especially with positive surgical margins).

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1. Introduction

Radical prostatectomy (RPE) provides high rates of local control in patients with prostate cancer [1]. It is commonly accepted that surgery achieves optimal results in patients with organ-confined disease. However, as soon as the organ capsule is penetrated, control rates drop significantly [2–4].

Several nomogram systems allow a rough appraisal of the probability of organ-confined cancer; however, they do not allow for any diagnostic conclusions for individual patients [5,6].

Despite all research efforts, none of the available preoperative staging measures developed for patients with prostate cancer facilitate a precise distinction between histopathological T2 and T3 cases. Thus, even after optimal clinical staging, a proportion of patients initially assumed to have organ-confined prostate cancer will suffer from pT3 prostate cancer.

In this regard, extracapsular extension (ECE) after RPE is reported to be present in roughly 38% to 52% of patients [7,8]. In addition, a proportion of those patients will also have positive surgical margins (R1) after pathological analysis of the tissue specimens.

Although in single-centre studies the survival outcome of patients with a pT3/pT4 carcinoma is favourable after 15 yr [9], surgery does not seem to be sufficient as the sole treatment mode. This is reflected by the fact that in the adjuvant setting ~38% of patients received hormonal treatment and ~19% of patients received radiation therapy (RT), respectively. Furthermore, in ~33% and ~19% of the cases, respectively, hormonal treatment or RT has been used in a salvage setting [9]. This implies that ~40% of those patients finally received RT. The aim of the current study is to review the present data with special emphasis on large randomised trials.

2. Methods

Relevant publications were detected by searching the Medical Literature Analysis and Retrieval System Online (MEDLINE) and the Public/Publisher MEDLINE (PUBMED; National Library of Medicine journal articles database) databases using the medical subject headings ''prostatic neoplasms,'' ''radiotherapy,'' ''adjuvant.'' A major emphasis was placed on the results of randomised trials. In addition, the Scopus database was used for cross-referencing. Conference proceedings from American Society of Clinical Oncology (ASCO)/American Society for Therapeutic Radiology and Oncology (ASTRO) between 2004 and 2007 and European Cancer Organisation (ECCO)/European Society for Therapeutic Radiology and Oncology (ESTRO) between 2004 and 2007 were included in the search.

3. Results

3.1. *Non-randomised trials*

There are numerous data available from non-randomised studies reporting on the outcome and toxicity of adjuvant radiotherapy (ART). Several retrospective series indicated that ART may significantly improve the biochemical no evidence of disease (bNED) rate and the disease-free survival rate, respectively.

The retrospective nature of these trials makes a final judgement difficult; the value of the data definitely increased with the use of PSA testing, more precise staging methods, and better RT techniques.

In Table 1 the results of several relevant series on outcome after ART are summarised [10–19]. Depending on the individual trial, increases in bNED rates of roughly 20–40% were reported.

3.2. *Randomised trials*

To clarify in how far a routinely applied ART in case of pT3 or R1 prostate cancer influences outcome, three multi-institutional trials were commenced 20 yr ago. The results of these trials were recently presented either as mature publications (eg, EORTC trial 22911 and SWOG trial 8794) [20–24] or as a presentations during major conferences (eg, German Intergroup trial number ARO 96-02/AUO AP 09/95) [25,26,28].

The EORTC trial [20–22] randomised 1005 pathologically node-negative patients after retropubic prostatectomy, including ilio-obturator lymphadenectomy (pT2–pT3; pN0M0 with R1, ECE or invasion of the seminal vesicles [SVI]) to either ''wait and see'' (observation group; 503 patients) or to receive ART with 60 Gy (502 patients).

The SWOG trial [23,24] randomised 425 prostate cancer patients with pN0/cN0 stage, ECE and/or SVI, or R1 to receive ART (60–64 Gy) versus observation (214 vs 211 patients). The surgical procedure included RPE; however, lymphadenectomy was not mandatory for patients considered to have a low risk of lymph-node involvement.

The results of the German Intergroup trial ARO 96-02/AUO AP 09/95 were presented at ASCO Annual Meetings in 2005 and in 2007 [25,28]. 385 patients with pT3pN0M0 prostate cancer were randomised 1 wk after surgery to the observation group or to receive ART. Patients with postoperatively undetectable prostate-specific antigen (PSA) levels (0.03–0.1 ng/ml; $n = 307$) who were randomised to the ART group received 60 Gy (5×2.0 Gy/wk; $n = 114$

Table 1 – Radical prostatectomy with or without adjuvant radiotherapy—retrospective/matched-pair analyses [10–19]

Study	Local control (%)		Disease-free survival (%)		Metastasis-free survival (%)		Survival (%)		Endpoint	Number of patients (total/+RT)
	RP	RP + RT	RP	RP + RT	RP	RP + RT	RP	RP + RT		
Anscher et al. 1995	60	92**	37	55	65	67	52	62	10 yr act.	159/46
Choo et al. 2002	98	100	65	88**	96	100	95	94	5 yr act.	125/73
Cozzarini et al. 2004	63	93**	31	69**	75	88**	80*	93* **	8 yr act.	415/237
Hawkins et al. 1995	87	98**	59	72**	–	**	~92	~92	5 yr act.	894/131
	–	–	35	63**	–	**	84*	98* **	10 yr act.	
Leibovich et al. 2000	≥84	100**	59	88**	≥84	100**	93	97	5 yr act.	152/76
Petrovich et al. 2001	–	–	66	70	–	–	91	91	5 yr act.	402/311
	–	–	46	53	–	–	~74	~81	10 yr act.	
Schild et al. 1996	83	100**	40	57**	~92	~92	92	~92	5 yr act.	288/60
Syndikus et al. 1996	79	100	74	93**	–	ns	89*	91*	5 yr act.	177/89
	50	91	40	74**					10 yr act.	
Valicenti et al. 1999	~92	~100	55	89**	–	–	–	–	5 yr act.	149/52
Vargas et al. 2005	~96	~97	47	57**	96	92	98*	100*	5 yr act.	617/133

* Cause-specific survival; ** statistically significant improvement with radiotherapy; ns = not significant.
RP = radical prostatectomy; RT = radiotherapy; yr = years; act. = actuarial.

[ART group]; $n = 159$ [observation group]; 21% of patients randomised to the ART group did not receive ART). Patients with detectable postoperative PSA levels ($n = 78$) were subsequently irradiated with 66.6 Gy (5×1.8 Gy/wk) and not included in the analysis.

In contrast, the EORTC trial included a small proportion of patients with detectable postoperative PSA levels; whereas, in the SWOG trial postoperative PSA testing was not mandatory. However, in the SWOG trial postsurgical PSA levels were available for 374 patients, and a second analysis of patterns of treatment failure among these patients was published in 2007 [24]. All trials included a small proportion of patients who had received neoadjuvant hormonal treatment. Details of characteristics of patients enrolled in these trials are shown in Table 2.

RT was started within 2–4 mo after surgery (EORTC trial median, 90 d; SWOG trial, within 18 wks, ARO/AUO trial, within 8–12 wks) with comparable treatment techniques, doses, and target volumes. (EORTC trial: ''Non-3D-planning with an isocentric technique, 50 Gy to a volume from the seminal vesicles to the apex with security margin, 10 Gy 'boost' to the previous landmarks of the prostate with a reduced security margin.'' SWOG trial: ''Non-3D-planning in four-field or arch technique included prostatic fossa, field size 9 cm × 9 cm or 10 cm × 10 cm, for the anterior–posterior portals, lateral portals with an attempt to block at least part of the rectum; 60–64 Gy.'' ARO/AUO trial: ''3D-planning included prostatic fossa and region of seminal vesicles +1 cm margin; 60 Gy.'')

The primary endpoints of the EORTC trial and the ARO/AUO trial studies were bNED rates. The primary endpoint of the SWOG trial was metastasis-free survival, while secondary outcomes included PSA relapse-free survival, recurrence-free survival (excluding PSA relapse), overall survival (OS), and freedom from hormonal treatment. Follow-up included PSA testing at intervals of 3 mo (SWOG and ARO/AUO trial) and 4 mo (EORTC trial) in the first year after surgery, followed by intervals of ≥6 mo. Different definitions of a biochemical relapse were employed: Whereas the EORTC trial defined any PSA-level increase of more than 0.2 ng/ml over the lowest postoperative value measured three times ≥2 wk apart as relapse, the SWOG trial defined any PSA level exceeding 0.4 ng/ml as failure. Within the ARO/AUO trial any increase from undetectable PSA to a detectable PSA level with a confirmation of a subsequent increase ≥3 mo later was considered as failure.

Median follow-up time for the EORTC trials was 5 yr; median follow-up time for the SWOG trial was 10.6 yr; and the median follow-up time for the ARO/AUO trial was presented after 40/53.6 mo (for the ART group) and 38.5/53.7 mo (for the observation group).

The EORTC trial reported 351 failures (131 in the ART group vs 220 in the observation group). The bNED rates revealed a significant benefit for the ART group versus the observation group, with bNED rates of 74.0% and 52.6%, respectively ($p < 0.0001$). Clinical progression-free survival rate was also significantly improved in the ART group (~87% in the ART group vs ~78% in the observation group; $p = 0.0009$).

Table 2 – Radical prostatectomy (RP) with or without adjuvant radiotherapy (ART): randomised trials [22–26]

Treatment group	EORTC		SWOG		ARO 96-02/AUO AP 09/95[+]	
	RP	RP + RT	RP	RP + RT	RP	RP + RT
Patients						
Number (*n*)	503	502	211	214	159[***]	114[***]
Median age (yr) (range)	65 (61–69)	65 (61–69)	65.8 (47.4–79.2)	64.1(43.8–78.0)	–	–
Neoadjuvant hormonal therapy	51 (10.1%)	50 (10.0%)	17 (8%)	19 (9%)	partly	partly
N category (patients in %)						
pN0	99.4	98.6	–	–	100	100
pN+	0.0	0.4	–	–	–	–
pNX	0.4	0.4	–	–	–	–
Missing	0.2	0.6	–	–	–	–
pN0/cN0	–	–	100	100	–	–
Pathological grade (patients in %)						
G1 (EORTC)/Gleason score ≤6 (SWOG)	11.3	13.7	36.0	43.9	–	–
G2 (EORTC)/Gleason score = 7 (SWOG)	65.0	60.4	28.9	26.2	–	–
G3 (EORTC)/Gleason score 8-10 (SWOG)	22.9	24.3	14.7	9.3	–	–
Missing	0.8	1.6	20.4	20.6	–	–
PSA level before surgery (ng/ml)						
Median (range)	12.4(7.2-20.0)	12.3(7.2–20.6)	–	–	–	–
PSA <10 ng/ml (patients in %)	–	–	53[**]	51[**]	–	–
PSA ≥10 ng/ml (patients in %)	–	–	47[**]	59[**]	–	–
PSA level after surgery (patients in %)						
0.03–0.1 ng/ml (ARO/AUO)					100	100
<0.2 ng/ml (within 3 weeks after surgery) (EORTC)	68.6	70.3				
≤0.2 ng/ml (SWOG)			57.3[++]	56.5[++]	–	–
0.2 ng/ml (3 wk after surgery but ≤0.2 later before relapse or further treatment) (EORTC)	18.9	19.5	–	–	–	–
Remained >0.2 ng/ml (EORTC)	12.3	9.2	–	–	–	–
>0.2 ng/ml and <1.0 ng/ml (SWOG)			20.9[++]	26.6[++]	0	0
>1.0 ng/ml (SWOG)			8.5[++]	5.1[++]	0	0
Unknown	0.2	1.0	13.3	11.7	0	0
Individual risk factors					all pT3	all pT3
Capsule perforation	78.9	75.1	–	–	–	–
Positive surgical margin	63.0	62.2	–	–	–	–
Capsule perforation or positive surgical margin	–	–	68	67	–	–
Invasion of seminal vesicles (SVI)	25.4	25.5	–	–	–	–

Table 2 (*Continued*)

Treatment group	EORTC		SWOG		ARO 96-02/AUO AP 09/95[+]	
	RP	RP + RT	RP	RP + RT	RP	RP + RT
Combination of risk factors					–	–
No risk factor	0	0.4	–	–	–	–
Capsule perforation only	25.2	27.7	–	–	–	–
SVI only	3.8	4.6	11	10	–	–
Positive margin only	15.7	16.7	–	–	–	–
Capsule perforation and SVI	8.0	5.2	–	–	–	–
Capsule perforation and positive margin	33.6	29.7	–	–	–	–
SVI and positive margin	1.6	3.2	–	–	–	–
All three risk factors	12.1	12.5	21	23	–	–

Endpoint	5 yr	5 yr	5 yr	10 yr	5 yr	10 yr	5 yr	5 yr
Biochemical progression-free survival (%)	52.6	74.0	~44	~28	~73	~52	54	72
PSA (ng/ml) after surgery subgroups:								
≤0.2 (EORTC) within 3 weeks	59.6	78.8						
>0.2 (EORTC) within 3 weeks	37.6	62.6						
≤0.2 (SWOG)[++]			~46	~27	~78	~58		
>0.2 and <1.0 (SWOG)[++]			~22	~20	~36	~28		
>1.0 ng/ml (SWOG)[++]			0	0	0	0		
0.03–0.1 (ARO/AUO, all patients)							54	72
Locoregional failure (%)	15.4	5.4		22[++]		8[++]	–	–
Distant failure (%)	6.3	6.3		16[++]		7[++]	–	–
Recurrence-free survival (%)	–	–	~69		~84		–	–
Metastasis-free survival (%)	–	–	~84*	~63*	~87*	~72*	–	–
Initiation of hormonal therapy (%)	–	–	21		10		–	–
Overall survival (%)	93.1*	92.3*	~90*	~67*	~91*	76*	–	–

EORTC: European Organization for Research and Treatment of Cancer trial number 22911; SWOG: Southwest Oncology Group trial number 8794; ARO 96-02/AUO AP 09/95: German Intergroup trial number ARO 96-02/AUO AP 09/95; PSA: prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy.

[+] No mature publication (available as abstracts); *not significant; **n = 302 with data; [++]n = 374 with data [24]; *** treatment per protocol.

The cumulative rate of locoregional failures was significantly lower after RT (5.4% in the ART group vs 15.4% in the observation group; $p < 0.0001$). The ARO/AUO trial reported bNED rates at 4 yr of 81% in the ART group and 60% in the observation group; bNED rates at 5 yr were 72% in the ART group and 54% in the observation group ($p = 0.0015$) for the collective treated per protocol.

The SWOG trial demonstrated a significant reduction of PSA relapse rates associated with ART. The median PSA relapse-free survival period was 10.3 yr in the ART group versus 3.1 yr in the observation group; bNED rates at 5 yr were ~73% in the ART group versus ~44% in the observation group. A significant reduction of recurrence of disease occurred in the ART group. The median recurrence-free survival period for the ART group was 13.8 yr versus 9.9 yr for the observation group.

The difference in the metastasis-free-survival rate was marginally significant in the SWOG trial. After 10 yr the metastasis-free-survival rate was ~72% for the ART group versus 63% for the observation group ($p = 0.06$). A significant difference in OS rates was not observed. However, a subsequent analysis of patients with available postsurgical PSA levels revealed that treatment failures at all postsurgical PSA levels (≤0.2 ng/ml vs 0.2–≤1.0 ng/ml vs >1.0 ng/ml) were predominantly local, with a low incidence of metastatic failure. Nevertheless, in accordance with the first analysis, ART reduced the percentage of patients with metastasis from 16% to 7% and the percentage of patients with clinical local failures from 22% to 8% over the observation group (Table 2) [24]. The difference with regard to the number of patients suffering from metastasis was highly significant between the two groups ($p < 0.01$).

The EORTC trial revealed no significant differences for the distant failure endpoints. (The rate of distant failure for the ART group was 6.1% vs 6.3% for the observation group, and OS was 92.3% in the ART group versus 93.1% in the observation group.)

Despite no influence on overall and borderline influence on metastasis-free survival rates, the SWOG trial provided evidence that ART significantly improved freedom from hormonal treatment. After 5 yr, 10% of patients in the ART groups had received hormonal treatment versus 21% of patients from the observation group.

The subgroup analyses performed within the EORTC trial and within the SWOG trial demonstrated a significant treatment effect on bNED rate for all subgroups (EORTC stratification: ECE, SVI, R1, PSA level after surgery ≤0.2 ng/ml, PSA level after surgery >0.2 ng/ml; SWOG stratification: ECE or R1, SVI, both pathologic findings). However, in a subsequent subset analysis of 552 EORTC trial patients, the R-status risk factor as assessed by reviewing pathology was the strongest predictor of prolonged biochemical disease-free survival with ART [21].

Importantly, the comparison of the central review data with those of the local pathologists indicated a high concordance for SVI (94%). However, less agreement was reported for ECE (57.5%) and for R-status (69.4%) [27].

The risk factor for postive surgical margin caused a statistically significant interaction with the treatment effect to such an extent that the treatment benefit in R0 patients was no longer significant. None of the following parameters had a statistically significant impact: localisation of positive margins, postoperative PSA, Gleason sum, SVI, and ECE [21].

With regard to the extent of positive surgical margins (apex or lateral or both), there was a trend toward a larger benefit for patients with positive margins in both localisations.

A preliminary subgroup analysis of the ARO/AUO trial [28] revealed that a statistically significant benefit was detectable for patients with R1, for patients with a preoperative PSA level >10 ng/ml, a Gleason score of 8, and a tumour of stage pT3b. Central pathology reassessment is currently being performed; data are not yet available.

Since the efficacy of any adjuvant treatment has to be balanced against its side-effects, analysis of treatment toxicity is important for the interpretation of these clinical trials. In this regard, toxicity was not documented prospectively during the SWOG trial. A retrospective chart analysis revealed that side-effects were more common in patients undergoing ART (total, 23.8% of patients receiving ART vs 11.9% of patients in the observation group; rectal, 3.3% vs 0%, respectively; urethral stricture, 17.8% vs 9.5%, respectively; urinary incontinence, 6.5% vs 2.8%; respectively).

During the EORTC trial, side-effects were documented prospectively using the World Health Organization (WHO) and the Radiation Therapy Oncology Group (RTOG) criteria for early side-effects and late side-effects (Tables 3a and 3b). RT was associated with an increased risk of immediate and late grade 1–2 side-effects; grade 3 side-effect rates were reported in <5% of the patients in both groups. The preliminary results of the ARO/AUO trial revealed that side-effects were rare and not pronounced (grade 3, genitourinary, acute toxicity in 3% of patients). Late side-effects (grade 3) were seen in 2% of patients (genitourinary); late rectal side-effects (grade 2) occurred in 1% of patients, respectively.

Table 3a – Selected early toxicity criteria from the Radiation Therapy Oncology Group (RTOG)

RTOG Criterion/Grade	0	1	2	3	4
Lower GI-tract including pelvis	No change	Increased frequency or change in quality of bowel habits not requiring medication; rectal discomfort not requiring analgesics.	Diarrhea requiring parasympatholytic drugs (eg, diphenoxylate); mucous discharge not necessitating sanitary pads; rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support; severe mucous or blood discharge necessitating sanitary pads; abdominal distension (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
Genitourinary	No change	Frequency of urination or nocturia twice pre-treatment habit; dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour; dysuria, urgency, bladder spasm requiring local anesthetic (e.g. phenazopyridine)	Frequency with urgency and nocturia hourly or more frequently; dysuria, pelvic pain, or bladder spasm requiring regular, frequent narcotic; gross hematuria with or without clot passage	Hematuria requiring transfusion; acute bladder obstruction not secondary to clot passage, ulceration or necrosis

Table 3b – Selected late toxicity criteria from the Radiation Therapy Oncology Group (RTOG)

RTOG Criterion/Grade	0	1	2	3	4
(Lower GI Tract) Small/large intestine	None	Mild diarrhea and colic; bowel movement 5× daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5× daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis; perforation; fistula
Ureter and bladder	None	Slight epithelial atrophy; minor teleangiectasia (microscopic hematuria)	Moderate frequency; generalized teleangiectasia, intermittent macroscopic hematuria	Severe frequency and dysuria; severe generalised teleangiectasia (often with petechiae); frequent hematuria; bladder capacity reduction <150–100 cm^3	Necrosis; contracted bladder (bladder capacity <100 cm^3); severe hemorrhagic cystitis
Hematuria	None	Slight microscopic hematuria	Macroscopic hematuria without clot passage	Macroscopic hematuria with clot passage	Massive bleeding requiring blood transfusion

Quality of life was assessed in a subgroup of the SWOG trial, but a detailed analysis is not yet available. Thus the impact of ART on quality of life is not yet known.

4. Discussion

In summary, the data from the randomised trials concordantly show that ART improves bNED rates and local control in patients with locally advanced prostate cancer after RPE. Since three different prospective trials support this statement, these results reflect the highest level of evidence (level of evidence 1). In accordance with the results obtained in most of the retrospective trials, by omitting ART, the risk of a biochemical failure is approximately doubled. Thus, the efficacy of ART of the prostate bed in order to eradicate microscopic residual tumour-cell deposits has to be considered as proven. Although the available data support clinical decision-making to some extent, several critical issues are not readily solved.

4.1. *Patient selection*

Since no clear-cut benefit in terms of OS was detectable for the whole collective and the influence on metastasis-free survival was marginally significant, the most important and obvious question is which individual patient will have a relevant benefit from an ART.

It is of special importance to bear in mind that a biochemical relapse per se is not a life-threatening event (even though it can lead to a state of steady anxiety considerably worsening the quality of life of patients). Thus it seems to be important to take into account how much the rates of metastases and secondary hormonal manipulations could be influenced by ART.

In general, local control after RPE depends on the presence and extent of ECE, SVI, R1, an unfavourable Gleason score, and a high preoperative PSA level [2,29–34]. Although all of these factors are of crucial importance for the selection of patients, they were not used for stratification in any of the trials. However, data on subgroups are available.

Putatively the greatest benefit from local radiation will be achieved in those patients with a comparatively low risk of distant seeding and a simultaneously high risk for residual tumour in the prostate bed. Since the predictors for local relapse and distant seeding are partially overlapping, these reflections remain theoretical and thus are not helpful for clinical decisions.

Regarding the individual prognostic factors, the available data on certain subgroups revealed that a proportionally similar increase in bNED rates was detectable for many of the risk factors.

Intuitively, one might take for granted that a positive residual tumor (R) status is a clear indicator for residual disease in the prostatic fossa. In this regard, controversial observations have been published [35,36]. Most notably the extent of positive surgical margins seems to be important for the prediction of biochemical progression after RPE. In a retrospective analysis of 76 patients with pT3 stage and a Gleason score of 7, Valicenti et al [37] found that the bNED rate was 92% for patients with focally positive surgical margins versus 58% for those with extensive positive surgical margins. By definition, positive margins were characterised as extensive whenever cells positive for cancer were seen in more than one high-powered microscopic field. After 5 yr patients with extensive positive surgical margins had bNED rates of 73% after ART versus 31% in those patients who did not receive RT. Similarly, D'Amico [38] provided evidence for higher local relapse rates whenever margins were diffusely positive and stated that some of the focally positive margins may have been artifactual [38–39].

In this context, the subset analysis of the EORTC trial with pathology review published in 2007 [21] is of special importance. First, the data indicate that a substantial variation among observers exists not only for grading but also for pathological staging and R status in prostate cancer. Secondly, after a central pathology review the only predictive factor for the efficacy of ART was a positive surgical margin. Thus, the authors conclude that ART might not be recommended in general for patients with negative surgical margins. Importantly, the authors did not differentiate between focally positive surgical margins versus extensively positive surgical margins.

Besides the pathological determination of residual disease, the postoperative PSA level may serve as marker for residual tumour activity. Unfortunately the postoperative PSA measurement is not helpful in distinguishing between local and distant residual disease.

With regard to the postsurgical PSA level, the inclusion criteria for all three randomised trials are heterogeneous to some extent. The German Intergroup trial required undetectable postoperative PSA levels for study enrollment, whereas the majority of the patients enrolled in the EORTC trial and the SWOG trial had undetectable PSA levels. In addition, PSA levels have not been documented completely for all patients in the SWOG trial. Of special importance is the fact that the EORTC trial and the SWOG trial

included patients with a detectable PSA level, whereas the German Intergroup trial treated these patients in a separate group. Since a substantial proportion of patients with an assumed benefit were removed from the analysis in the German Intergroup trial, considerable bias is added (EORTC trial, 5-yr bNED rate: 74.0% of patients in the ART group vs 52.6% of patients in the observation group; SWOG trial, 5-yr bNED rate: ~73% vs ~44%, respectively; and German Intergroup trial, 5-yr bNED rate: 72% vs 54%, respectively).

4.2. *Adjuvant versus salvage radiotherapy*

As stated above, adequate selection of patients for ART is still hampered by the lack of strong predictors. Thus, some clinicians tend to favour a ''wait-and-see'' policy after RPE. In order to avoid possible side-effects of ART, this policy might be suitable for a proportion of these patients. However, a matched-pair analysis supports the notion that this strategy might be problematic. In this regard Valicenti et al [40] presented their matched-pair analysis of adjuvant (within 12 mo) and salvage (median pretherapeutic PSA level, 0.6 ng/ml) RT for pT3/pT4 prostate cancer in 316 patients with initially undetectable postoperative PSA levels. After controlling for prognostic factors by the matching procedure, there was a significant improvement in long-term PSA control with early ART versus delayed salvage RT. The 5-yr bNED rates were 68% of patients in the ART group and 42% of patients in the salvage RT group. Further significant factors based on multivariate analyses associated with lower bNED rates were SVI and Gleason scores >7.

In this context, retrospective data concerning the efficacy and predictive factors of salvage RT are available [41–43]. Stephenson et al [43] demonstrated that pretherapeutic PSA levels <0.6 ng/ml resulted in significantly improved local control rates. Furthermore it could be shown that higher Gleason scores, higher PSA levels before initiating RT, a short PSA doubling time, SVI, and negative surgical margins were associated with unfavourable bNED rates. This basically reflects the fact that these factors are also independent predictors also for distant failure.

Although the prospective trials have not conclusively documented the influence of ART on the development of secondary metastasis, there is still substantial evidence that local failure is associated with a higher risk for metastases whenever the follow-up is long enough. Stephenson et al provided evidence that salvage RT strongly reduced the risk for metastatic progression [44]. This observation is corroborated by retrospective data on local failure after definitive radiation of localised prostate cancer revealing a secondary ''late'' wave of metastasis from the uncontrolled local tumour [45]. In this context, the analyses of predominant treatment failure in the EORTC trial and the SWOG trial are of special importance. Both trials revealed that in high-risk patients the predominant pattern of treatment failure is local, with a surprisingly low incidence of metastatic failure. Thus, improving local control will have a large impact on outcomes in patients at high risk after RPE.

Since hormonal treatments impose a relevant risk of side-effects [46,47], are not curative, and have relevant socioeconomic consequences, the reduced necessity of hormonal treatment after ART has to be considered in decision-making.

A proportion of patients initially randomised to the observation group finally received salvage RT (EORTC trial, 113 of 207 patients; SWOG trial, 70 of 211 patients; German Intergroup trial, unknown). Thus it is evident that the outcome data are biased by these crossover patients. Therefore—without the willingness to dilute the prominence of those trials—none of the studies will finally solve the question of the extent to which early ART or salvage RT result in better outcomes.

Further multicentre trials regarding the optimal adjuvant treatment of locally advanced prostate cancer including RT are projected by the EORTC, the German Cancer Society, and the Medical Research Council (MRC) Clinical Trial Unit (Radiotherapy and Androgen Deprivation in Combination after Local Surgery [RADICALS], early ART vs salvage RT and duration of hormonal therapy vs lack of hormonal therapy).

4.3. *Radiation dose*

Based on the results of the prospective trials, a radiation dose of 60 Gy can be regarded as effective in the early adjuvant setting. Although clear dose–response relationships have been documented for the RT of prostate cancer in a primary setting [48], no prospective data are available for ART. However, retrospective series suggest dose–response relationships for both the adjuvant setting [49] and the salvage setting [50]. Valicenti et al stated that radiation doses >61.5 Gy were associated with a significantly improved bNED rate in patients with postoperatively undetectable PSA levels [49]. Moreover, in a recently published analysis, King et al [51] postulate that ''a clinically significant gain in biochemical relapse-free survival (bRFS) would be achieved with doses greater than that currently

recommended for . . .'' ART. Based on their estimates of an expected proportional gain in the bRFS rate of ~3% per incremental Gray, the authors advocate the need for a randomised trial that would test two different ART doses (60 Gy vs 66 Gy).

4.4. *Concomitant hormonal treatment*

In contrast to the documented role of a concomitant and adjuvant hormonal ablation for high-risk or lymph-node-positive prostate cancer [52–56], the value of hormonal ablation in the ART setting is poorly defined. In this regard, the results of RTOG study 96-01, which is evaluating the use of long-term (2-yr) hormonal monotherapy (bicalutamide) in combination with ART (64.8 Gy), are eagerly awaited. (Patient accrual was finished in 2003.)

Presently there is evidence that an adjuvant hormonal therapy alone improves long-term outcome for node-negative patients with locally advanced prostate cancer after RPE. Thus, the decision to complement RT by an adjuvant hormonal ablation can only be made after individual risk assessment.

5. Conclusions

Based purely on evidence criteria, ART has to be regarded as the gold standard for those patients with a reasonablely high risk of local relapse but with a comparatively low risk of distant seeding. Since the determination of such a risk remains difficult, both the identification of new predictive factors and high-quality pathological analyses [57] are of utmost importance for the future.

Currently, the only endpoints found to be influenced by ART were bNED rate, local control, freedom from hormonal treatment, and, to a lesser extent, metastasis-free survival rate. Presently, OS has not been significantly influenced.

Based on the data presented, we conclude that for any patient with an R1 resection, pT3, or persisting PSA level, interdisciplinary counsel among the radiation oncologist, the urologist, and the pathologist is mandatory. In addition, we are convinced that, based on the reviewed data, all patients must be adequately informed about the beneficial effects of RT in locally advanced prostate cancer. Furthermore, we find it justified to consider ART of the prostate bed to be standard for all cases with positive surgical margins or persisting PSA levels. For individualised decisions, additional histopathological features namely tumour stage ≥T3, grading, perineural invasion, lymphangiosis, or venangiosis should be taken into account (Fig. 1).

In highly select cases a ''wait-and-see'' policy seems to be suitable, provided that an informed decision has been reached and that close monitoring of PSA levels takes place, permitting an early salvage RT where indicated. Furthermore we find it important to note that in the future all other adjuvant

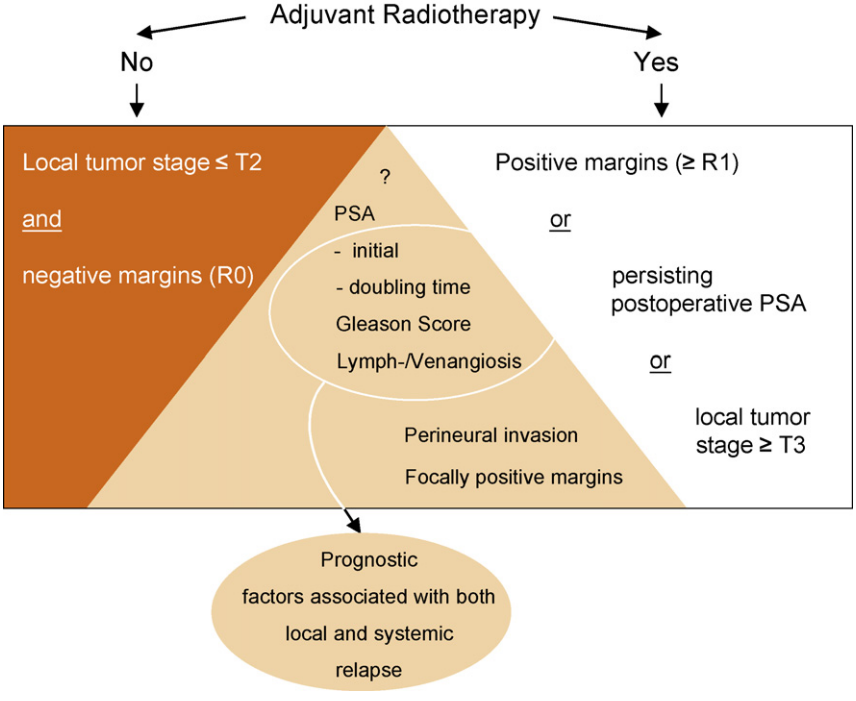

Fig. 1 – Factors influencing clinical decision making.

treatment approaches must be validated against the proven efficacy of ART.

The identification of predictive factors will be the key issue for current and future research. In this regard, complex genome, or proteome analyses of relevant signalling pathways, for example the PKB/Akt cascade, could enable a better risk stratification [58].

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Study concept and design: Ganswindt, Belka.
Acquisition of data: Ganswindt, Belka.
Analysis and interpretation of data: Ganswindt, Belka, Stenzl, Bamberg.
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Editorial Comment on: Adjuvant Radiotherapy for Patients with Locally Advanced Prostate Cancer—A New Standard?

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Ganswindt et al critically reviewed [1] the available data from three randomised trials (EORTC 22911, SWOG 8794, and ARO 96-22/AUO AP 09/95), definitively proving the efficacy of standard-dose adjuvant radiotherapy (ART) after radical prostatectomy (RPE) in at least halving the risk of biochemical and local failure, as well as the need for salvage hormonal therapy in node-negative, high-risk prostate cancer patients (HRPC).

Some other issues, however, remain unresolved: first, whether timely salvage irradiation (ie, with PSA value <0.5–0.6 ng/ml) could in the near future replace mass irradiation, especially when extracapsular perforation or surgical margin infiltration is only ''focal.'' This approach would spare at least 40–50% of patients currently candidate to ART unnecessary irradiation.

Second, the recent awareness that the risk of failure in HRPC patients not undergoing ART after RP is predominantly local, with a surprisingly low incidence of distant metastases [2], raises the key issues of the optimal dose of ART and of the role of adjuvant androgen deprivation (AAD). Randomised trials testing dose levels higher than those currently adopted are awaited [3], given the reasonable hope that three-dimensional radiotherapy (not in routine use in the above-mentioned studies) and more recently available intensity-modulated techniques may, despite a moderate dose-escalation, permit the toxicity profile of ART to remain acceptable. Similarly, randomised studies investigating the real clinical benefit deriving from AAD concomitant to ART for a disease with a proven extremely low propensity to systemic spread are no longer deferrable.

Moreover, the trials herein discussed did not analyze the impact of ART on postsurgical erectile function recovery. The increasing diffusion of nerve-sparing prostatectomy (NS-RP) is resulting in greater numbers of younger, potent men being potential candidates for ART. Intensity-modulated ART [4], coupled with MRI simulation for better individualisation and sparing of erectile tissue [5], should permit delivery of a truly ''nerve and bulb-sparing'' ART to those patients with good chances of erectile function recovery after NS-RP.

Finally, hypofractionated regimens may soon reduce the high socioeconomic cost to both patients and healthcare systems [6] of a conventionally fractionated ART.

The future of adjuvant radiotherapy appears to be just around the corner.

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Editorial Comment on: Adjuvant Radiotherapy for Patients with Locally Advanced Prostate Cancer—A New Standard?

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This is a nice review article by Ganswindt et al on the role of adjuvant radiotherapy (ART) following radical prostatectomy for locally advanced prostate cancer [1].

The three major randomised studies dealing with this issue—EORTC 22911, SWOG 8794, and ARO 96-02/AUO AP 09/95—have demonstrated that biochemical progression-free survival and local control are significantly improved by ART with 60–64 Gy if prognostic factors for local recurrence are evidenced in the pathological specimen. Among these, positive surgical margins emerged as the strongest predictors of prolonged disease-free survival, whereas it was not possible to demonstrate the same significant impact of ART on pT3a disease with negative margins [2].

Based on these findings, it can be undoubtedly concluded that ART for locally advanced prostate cancer can be considered a clinical standard. Nonetheless, several issues, only partially mentioned by the authors, still remain to be investigated.

Dose escalation. Can results reported be further improved by increasing total dose delivered to the prostatic fossa without significantly increasing acute and late complications?

Late complications and quality of life. Although acute toxicity associated with ART has been properly investigated in the three major studies, little has been reported on long-term complications and quality of life related to this treatment modality.

Adjuvant versus salvage radiotherapy. It is unquestionable that disease progression does not occur in all patients with locally advanced prostate cancer following surgery. Theoretically, a potential harmful treatment such as ART could be indicated only at biological disease progression. Previous experience with salvage radiotherapy has not demonstrated the same good outcome obtained with ART, but it was conducted for late PSA recurrences or even for clinical evidence of local recurrence [3]. Earlier salvage therapy could perhaps obtain results more similar to those obtained with ART with the great advantage of selecting for treatment only patients who really need it.

Adjuvant radiotherapy for node-positive patients. Because it has been clearly demonstrated that a large subset of patients with limited nodal involvement experience long-term biological disease-free survival after radical prostatectomy and can be considered affected by a locally advanced rather than systemic disease [4,5], it is consequen-

tial to postulate that this subset of patients might also benefit from ART.

These are the hot topics related to ART for locally advanced prostate cancer—and they will hopefully be the object of future clinical studies and reports.

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