6.3.Management of PSA-only recurrence after treatment with curative intent

The follow up policy is described in chapter 7 and will not be discussed here.

6.3.1.Background

Between 27% and 53% of all patients undergoing RP or RT develop PSA recurrence. Whilst a rising PSA level universally precedes metastatic progression, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a measurable PSA may not necessarily lead to clinically apparent metastatic disease. Physicians treating patients with PSA-only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding over-treating patients whose disease may never affect their OS or QoL. It should be emphasised that the treatment recommendations for these patients should be given after discussion in a multidisciplinary team.

6.3.2.Definitions of clinically relevant PSA relapse

The PSA level that defines treatment failure depends on the primary treatment. Patients with PSA-recurrence after RP or primary RT have different risks of subsequent symptomatic metastatic disease. Therefore, physicians should carefully interpret BCR endpoints when comparing treatments.

After RP, the threshold that best predicts further metastases is a PSA > 0.4 ng/mL and rising [583-585] However, with access to ultra-sensitive PSA testing, a rising PSA much below this level will be a cause for concern for patients. After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of > 80% for clinical failure) is any PSA increase ≥ 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir [586].

After HIFU or cryotherapy, no endpoints have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of an acceptable PSA threshold after these alternative local treatments.

6.3.3.Natural history of biochemical recurrence

Once a PSA relapse has been diagnosed, it is important to determine, as far as possible, whether the recurrence has developed at local or distant sites. The risk of subsequent metastases and PCSM may be predicted by the initial clinical and pathologic factors (e.g. T-category, PSA, GS) and PSA kinetics (PSA-DT and interval to PSA failure).

6.3.3.1.Post-radical prostatectomy biochemical recurrence

Not all patients with BCR after RP will develop clinical recurrences. In two studies of 1,997 and 2,400 men treated by RP, only 23-34% of those with BCR developed a clinical recurrence and 6% subsequently died of PCa [569,587].

Several studies have attempted to identify risk factors for metastases and PCSM in patients experiencing PSA-only recurrence following RP. A PSA-DT < three months, SVI (pT3b), specimen GS 8-10, or time to PSA recurrence < 3 years indicate a high risk of metastases and PCSM. Conversely, a PSA-recurrence > three years following surgery, specimen GS < 7, pathologic organ-confined disease or limited extracapsular extension (pT3a), and PSA-DT > twelve months indicates a low risk of metastases and PCSM [588-591]. A rising PSA-DT, ≤ 0.2 ng/mL, has been associated with an increased risk of metastases and death [592]. Patients in the low-risk subgroup typically respond very well to SRT with a high probability of PSA being undetectable [593]. However, it must be stressed that most patients within the low-risk subgroup have an excellent outcome even without any salvage treatment. Patients within the high-risk subgroup need early and aggressive salvage treatment [594]. Trock et al. demonstrated that SRT was associated with a significant three-fold increase in PCa-specific survival relative to those who received no salvage treatment. The increase in PCa-specific survival associated with SRT was limited to men with a PSA-DT of < six months and remained after adjustment for pathological stage and other established prognostic factors. Salvage RT initiated > two years after recurrence provided no significant increase in PCa-specific survival [594].

6.3.3.2.Post-radiotherapy biochemical recurrence

In patients experiencing PSA-recurrence after RT, PSA-DT < three months, time to biochemical progression < three years, biopsy GS 8-10 or clinical stage cT3b-T4 also indicate a high risk of metastases and PCSM. Conversely, PSADT > fifteen months, biopsy GS < 7, clinical stage < cT3a and time to BCR > three years indicate a low risk of metastases and PCSM [590,595,596].

Zumsteg et al. have designed a risk score to further subdivide patients who develop PSA recurrence following RT. Those with > two high-risk factors (PSA-DT < three months, time to BCR < three years, biopsy GS 8-10 and clinical stage cT3b-T4) have an increased risk of developing metastases and PCSM as compared to those with 0 or 1 risk factor [596].

6.3.4.The role of imaging in PSA-only recurrence

6.3.4.1.Assessment of metastases

6.3.4.1.1.Bone scan and abdominopelvic CT

Because BCR after RP or RT precedes clinical metastases by seven to eight years, on average [569,597], the diagnostic yield of common imaging techniques (bone scan and abdominopelvic CT) is low in asymptomatic patients [598]. In men with PSA-only relapse after RP, the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL [599,600].

Only 11-14% of patients with BCR after RP have a positive CT [599]. In a series of 132 men with BCR after RP, the mean PSA level and PSA velocity associated with a positive CT was 27.4 ng/mL and 1.8 ng/mL/month, respectively [601].

6.3.4.1.2.Choline PET/CT

In two different meta-analyses, the combined sensitivities and specificities of choline PET/CT for all sites of recurrence in patients with BCR were 86-89% and 89-93%, respectively [602,603].

Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [604] and may be positive for bone metastases in up to 15% of patients with BCR after RP and negative bone scan [605]. The specificity of choline PET/CT is also higher than bone scan with fewer false-positive and indeterminate findings [279]. Detection of LN metastases using choline PET/CT remains limited by the relatively poor sensitivity of the technique (see Section 5.3.2.2).

Choline PET/CT sensitivity is strongly dependent on the PSA level and kinetics [265,606-608]. In patients with BCR after RP, PET/CT detection rates are only 5-24% when the PSA level is < 1 ng/mL, but rises to 67-100% when the PSA level is > 5 ng/mL. In a recent meta-analysis, choline PET/CT detection rates were 65% (95% CI: 58%-71%) when the PSA-DT was < six months, and were 71% (95% CI: 66%-76%) and 77% (95% CI: 71%-82%) when the PSA velocity was > 1 and > 2 ng/mL/year, respectively [606].

Despite its limitations, choline PET/CT may change medical management in 18-48% of patients with BCR after primary treatment [609-611]. In a retrospective bi-centric study of 150 patients, 14 of the 55 (25.5%) patients scheduled for palliative treatment were switched to salvage therapy based on choline PET/CT results. Salvage therapy induced a complete biochemical response in 35.7% of these patients at the end of a median follow-up of 18.3 months (range, 10-48 months) [611].

Choline PET/CT cannot be recommended in all patients, but should be limited to patients who are fit enough for curative loco-regional salvage treatment.

After RP, the optimal PSA cut-off level for choline PET/CT analysis seems to be between 1 and
2 ng/mL [607,608]. It is unclear whether PSA velocity or PSA-DT thresholds can be used to further select groups of patients in whom PET/CT could be recommended.

After RT, the PSA cut-off level is unclear due to the lack of sufficient data and because the PSA level is more difficult to interpret due to the “physiological” amount of measurable PSA produced by the non-tumoural prostate [607]. In a study of 46 patients with PSA relapse after RT or brachytherapy, the choline PET/CT detection rate was 54.5%, 81%, 89% and 100% when the PSA level was 1-2 ng/mL, 2-4 ng/mL, 4-6 ng/mL and > 6 ng/mL, respectively [612]. In another study of 140 patients the choline PET/CT detection rate was not influenced by the PSA level, but only by PSA kinetics [613].

6.3.4.1.3.Fluoride PET and PET/CT

18F-Fluoride PET and PET/CT have a higher sensitivity than bone scan in detecting bone metastases [614]. However, 18F-Fluoride is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [615].

6.3.4.1.4.Prostate-specific membrane antigen-based PET/CT

Prostate-specific membrane antigen-based PET/CT has shown promising potential in patients with BCR, although most studies are limited by their retrospective design. Detection rates of 15-58%, 25-73% and 69-100%, 71-100% have been reported for PSA ranges of 0.2-0.5 ng/mL, 0.5-1 ng/mL, 1-2 ng/mL and > 2 ng/mL respectively [290,616-620]. In these PSA ranges, the relative proportion of positive findings corresponding to purely local recurrences or to distant metastases remains unclear. Nonetheless, PSMA PET/CT seems substantially more sensitive than choline PET/CT, especially for PSA levels < 1 ng/mL. Two head-to-head comparisons confirmed this finding [617,621]. PSMA PET/CT identified the site of recurrence in 14 of 32 patients with negative choline PET/CT (44%; prostatic bed, n=8; LNs, n=6) [622]. Higher PSA velocity or lower PSA doubling time seem associated with higher PSMA PET/CT positivity rates [275,290,616,623], even if some authors found no correlation between PSA kinetics and positivity rates [617].

In a prospective multicentre study of 323 patients with BCR, PSMA PET/CT changed the management intent in 62% of patients as compared to conventional staging. This was due to a significant reduction in the number of men in whom the site of disease recurrence was unknown (77% vs. 19%, $p < 0.001$) and a significant increase in the number of men with metastatic disease (11% vs. 57%) [289].

A single-centre study assessed 164 men who underwent PSMA PET/CT for rising PSA after RP, with PSA levels < 1 ng/mL. In men with a negative PSMA PET/CT who received salvage RT, 85% (n=23/27) demonstrated a treatment response, compared to further PSA increase in 65% (22/34) in those not treated. In the 36/99 men with disease confined to the prostate fossa on PSMA, 83% (n=29/36) responded to salvage RT [624]. Thus, PSMA PET/CT might stratify men into a group with high response (negative findings or recurrence confined to prostate) and poor response (positive nodes or distant disease) to salvage RT. However, these results based on small numbers and short follow-up should be confirmed in other studies.

6.3.4.1.5.Whole-body and axial MRI

Little is known regarding the accuracy of whole-body or axial MRI in patients with BCR after RP or RT [625]. Therefore, the role of these techniques in detecting occult bone or LN metastases in the case of BCR remains to be assessed.

6.3.4.2.Assessment of local recurrences

6.3.4.2.1.Local recurrence after radical prostatectomy

Because the sensitivity of anastomotic biopsies is low, especially for PSA levels < 1 ng/mL [598], salvage RT is usually decided on the basis of the BCR, without histological proof of the local recurrence, preferably when the PSA level is below 0.5 ng/mL. The dose delivered to the prostatic fossa tends to be uniform since it has not been demonstrated that a focal dose escalation at the site of recurrence improves the outcome. Thus, most patients undergo salvage RT without local imaging.

Multiparametric magnetic resonance imaging can detect local recurrences in the prostatic bed, but its sensitivity in patients with PSA level < 0.5 ng/mL remains controversial [626,627]. Choline PET/CT is less sensitive than mpMRI when the PSA level is < 1 ng/mL [628]. Prostate-specific membrane antigen-based PET/CT is positive in 15-58% of patients with BCR and PSA levels < 0.5 ng/mL [617,618,620], but published series are difficult to interpret since they usually mix patients with history of RP and RT and do not specify the proportion of local recurrences and distant metastases diagnosed at PSA levels < 0.5 ng/mL.

Precise detection and location of local recurrences after RP will be needed only if it is proven that stereotaxic boost to the recurrence site during salvage RT improves the patient outcome.

6.3.4.2.2.Local recurrence after radiation therapy

In patients with BCR after RT, the biopsy status is a major predictor of outcome, provided the biopsies are obtained 18-24 months after treatment. Given the morbidity of local salvage options it is necessary to obtain histological proof of the local recurrence before treating the patient [598].

Transrectal US is not reliable in depicting local recurrences after RT. In contrast, mpMRI has yielded excellent results [598,629-631] and can be used for biopsy targeting and guiding local salvage treatment. Detection of recurrent cancer is also feasible with choline PET/CT [613], but choline PET/CT has not been compared to mpMRI yet. It is also too soon to know if PSMA PET/CT can play a role in the detection of local recurrences after RT [275].

6.3.4.3.Summary of evidence on imaging in case of biochemical recurrence

Detection and localisation of the local recurrence site after RP is not necessary since it has not been proven that stereotaxic boost to the recurrence site during salvage RT improves the outcome.

It is necessary to confirm the local recurrence after RT by biopsy and to localise it as precisely as possible before salvage treatment. Multiparametric MRI is so far the best technique to localise the recurrence and guide the biopsy.

Many recent studies suggest that PSMA PET/CT is substantially more sensitive than abdominopelvic CT, bone scan and choline PET/CT in the detection of distant metastases in patients with BCR. Although most studies are retrospective and/or monocentric, they all came to the same conclusion. Early detection of metastases in a BCR setting is clinically highly relevant. This is particularly true in the post-RT setting. Salvage therapies for local recurrences after RT induce a substantial morbidity and it is necessary to detect metastatic patients with the highest possible sensitivity, to avoid the morbidity of useless salvage therapies in these patients. After RP, unlike choline PET/CT, PSMA PET/CT showed high positivity rates, even for PSA levels < 1 ng/mL. Because the localisation of the local recurrence is not useful, the indication of a sensitive test like PSMA PET/CT in patients with PSA levels < 1 ng/mL will depend on their risk of having metastatic disease. Prostate-specific antigen kinetics might be useful, but this needs to be proven.

6.3.4.4.Guidelines for imaging in patients with biochemical recurrence

Prostate-specific antigen (PSA) recurrence after radical prostatectomy	LE	Strength rating
Perform imaging only if the outcome will influence subsequent treatment decisions.		Strong
If the PSA level is ≥ 1 ng/mL, perform a prostate-specific membrane antigen positron emission tomography computed tomography (PSMA PET/CT), if available, or a choline PET/CT imaging otherwise.	2b	Weak
PSA recurrence after radiotherapy		
Perform prostate multiparametric magnetic resonance imaging to localise abnormal areas and guide biopsies in patients who are considered candidates for local salvage therapy.	3	Strong
Perform PSMA PET/CT (if available) or choline PET/CT imaging to rule out positive lymph nodes or distant metastases in patients fit for curative salvage treatment.	2b	Strong

6.3.5.Treatment of PSA-only recurrences

The timing and treatment modality for PSA-only recurrences after RP or RT remain a matter of controversy based on the limited evidence.

6.3.5.1.Salvage radiotherapy [SRT] for PSA-only recurrence after radical prostatectomy

Early SRT provides the possibility of cure for patients with an increasing or persistent PSA after RP. More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level [632-635], corresponding to a ~80% chance of being progression-free five years later [578]. A retrospective analysis of 635 patients who were followed after RP and experienced BCR and/or local recurrence and either received no salvage treatment (n=397) or salvage RT alone (n=160) within two years of BCR, showed that salvage RT was associated with a three-fold increase in PCa-specific survival relative to those who received no salvage treatment ($p < 0.001$). Salvage RT has also been effective in patients with a short PSA-DT [594]. Despite the indication for salvage RT, a “wait and see” strategy remains an option in patients with a long PSA-DT of > twelve months [587]. For an overview, see Table 6.3.1.

Table 6.3.1: Selected studies of post-prostatectomy salvage radiotherapy, stratified by pre-salvage radiotherapy (SRT) PSA level*

Reference	Year	n	Median FU (mo)	pre-SRT PSA (ng/mL) median	RT dose ADT	bNED/PFS (year)	5-yr results
Bartkowiak, *et al.* [636]	2017	464	71	0.31	66.6 Gy	54% (5.9)	73% vs. 56%; PSA < 0.2 vs. ≥ 0.2 ng/mL p < 0.0001
Tendulkar, *et al.* [637]	2016	2460	60	0.5	66 Gy 16% ADT	56% (5)	SRT; PSA ≤ 0.2 ng/mL 71% 0.21-0.5 ng/mL 63% 0.51-1.0 ng/mL 54% 1.01-2.0 ng/mL 43% > 2 ng/mL 37% p < 0.001
Stish, *et al.* [632]	2016	1106	107	0.6	68 Gy 16% ADT	50% (5) 36% (10)	44% vs. 58%; PSA ≤ 0.5 vs. > 0.5 ng/mL p < 0.001
Soto, *et al.* [638]	2012	441	36	< 1 (58%)	68 Gy 24% ADT	63/55% (3) ADT/no ADT	44/40% ADT/no ADT p < 0.16

*Androgen deprivation therapy can influence the outcome 'biochemically no evidence of disease (bNED)'
or 'progression-free survival'. Therefore, data sets without ADT are highlighted. To facilitate comparisons, 5-year bNED/PFS read-outs from Kaplan-Meier plots are included.

ADT=androgen deprivation therapy; bNED=biochemically no evidence of disease; FU=follow up; mo=months; n=number of patients; PFS=progression-free survival; PSA=prostate-specific antigen; SRT=salvage radiotherapy; yr=year.

Although biochemical progression is now widely accepted as a surrogate marker of PCa recurrence, metastatic disease, disease specific and OS are more clinically meaningful endpoints which are used to support clinical decision making. However, low event rates and the necessity for long-term follow-up limit the volume of available evidence, in terms both of statistics and of the effects of RT technical developments over time. Table 6.3.2 summarises results for recent studies on clinical endpoints after SRT.

Two studies report significantly better outcomes (DM, DSM and OS) in patients who re-achieve a PSA nadir < 0.1 ng/mL after SRT without ADT [636,639]. A recent, international, multi-institutional analysis of pooled data from RCTs has suggested that metastasis-free survival is the surrogate endpoint of most validity, in respect of its impact on OS [640].

Table 6.3.2: Recent studies reporting clinical endpoints after SRT

Reference	Year	n	Median FU (mo)	Regimen	Outcome
Tendulkar, *et al.* [637]	2016	2,460	60	66 (64.8-68.4) Gy incl. 16% ADT	10 yr DM SRT; PSA 0.01-0.2 ng/mL 9% SRT; PSA 0.21-0.50 ng/mL 15% SRT; PSA 0.51-1.0 ng/mL 19% SRT; PSA 1.01-2.0 ng/mL 20% SRT; PSA > 2 ng/mL 37%, p < 0.001
Stish, *et al.* [632]	2016	1106	107	68 (64.8-70.2) Gy 39% 2D treatment planning incl. 16% ADT	5 and 8.9 yr DM SRT; PSA ≤ 0.5 ng/mL 7% and 12% SRT; PSA > 0.5 ng/mL 14% and 23% p < 0.001 5 and 8.9 yr DSM SRT; PSA ≤ 0.5 ng/mL < 1% and 6% SRT; PSA > 0.5 ng/mL 5% and 10% p=0.02 5 and 8.9 yr OS SRT; PSA ≤ 0.5 ng/mL 94% and 86% SRT; PSA > 0.5 ng/mL 91% and 78% p=0.14

Jackson, *et al.* [639]	2014	448	64	68.4 Gy no ADT	5 yr DM post-SRT PSA < 0.1 ng/mL 5% post-SRT PSA ≥ 0.1 ng/mL 29% p < 0.0001 5 yr DSM post-SRT PSA < 0.1 ng/mL 2% post-SRT PSA ≥ 0.1 ng/mL 7% p < 0.0001 OS post-SRT PSA < 0.1 ng/mL 97% post-SRT PSA ≥ 0.1 ng/mL 90% p < 0.0001
Bartkowiak, *et al.* [636]	2017	464	71	66.6 (59.4- 72) Gy no ADT	5.9 yr OS post-SRT PSA < 0.1 ng/mL 98% post-SRT PSA ≥ 0.1 ng/mL 92% p=0.005

ADT=androgen deprivation therapy; DM=distant metastasis; DSM=disease specific mortality;

FU=follow up; mo=months; n=number of patients; OS=overall survival; PSA=prostate specific antigen; SRT=salvage radiotherapy.

Recent data from RTOG 9601 [641] suggested both CSS and OS benefits for adding two years of bicalutamide to SRT. According to GETUG-AFU 16, also six months treatment with gonadotropin-releasing hormone (GnRH) analogue can improve five-year PFS significantly, but a longer follow-up is required [642]. Both trials used outdated radiation dosages and technique. Table 6.3.3 gives an overview of these two RCTs. A recent literature review recommends risk stratification based on the pre-SRT PSA (> 0.7 ng/mL), margin status (positive), and high GS, to personalise the use of hormone therapy with SRT [643].

Table 6.3.3: RCTs comparing salvage radiotherapy alone and salvage radiotherapy combined with androgen deprivation therapy

Reference	Year	n	Risk groups	Median FU (mo)	Regimen	Outcome
GETUG-AFU 16 Carrie, *et al.* [642]	2016	369 RT + ADT 374 RT	GS ≤ 7 89%, GS ≥ 8 11% cN0	63	66 Gy + GnRH analogue 6 mo 66 Gy	5 yr PFS 80% p < 0.0001 5 yr PFS 62%
RTOG 9601 Shipley, *et al.* [641]	2017	384 RT + ADT 376 RT	pT2 R1, pT3 cN0	156	64.8 Gy + bicalutamide 24 mo 64.8 Gy + placebo	12 yr DM 14% p=0.005 12 yr DM 23% 12 yr OS 76% p=0.04 12 yr OS 71% 12 yr DSM 5.8% p < 0.001 12 yr DSM 13.4%

ADT=androgen deprivation therapy; DM=distant metastasis; DSM=disease specific mortality; GS=Gleason score; PFS=progression free survival; FU=follow-up; GnRH=gonadotropin-releasing hormone; OS=overall survival; PFS=progression-free survival; mo=months; n=number of patients; RT=Radiotherapy; yr=years.

6.3.5.1.1.Target volume, dose, toxicity

There have been various attempts to define common outlines for “clinical target volumes” of PCa [644-647] and for organs at risk of normal tissue complications [648]. However, given the variations of techniques and dose-constraints, a satisfactory consensus has not yet been achieved

The optimal SRT dose has not been well defined. It should be at least 66 Gy to the prostatic fossa (plus/minus the base of the seminal vesicles, depending on the pathological stage after RP) [633,649]. A USA Guideline Panel regarded 64-65 Gy as the minimum dose that should be delivered post RP [650]. However, more recent data suggest that higher total doses can achieve higher rates of biochemical control at three to five years [651]. In a SR, the pre-SRT PSA level and SRT dose both correlated with BCR, showing that relapse-free survival decreased by 2.4% per 0.1 ng/mL PSA and improved by 2.6% per Gy, suggesting that a treatment dose above 70 Gy should be administered at the lowest possible PSA level [652]. The combination of pT stage, margin status and GS and the PSA at SRT seems to define the risk of biochemical progression, metastasis and overall mortality [653-655]. The updated Stephenson nomograms incorporate the SRT-dose and ADT as predictive factors for biochemical failure and distant metastasis [637]. In a study on 894 node-negative PCa patients, sufficient doses ranging from 64 to ≥ 74 Gy were assigned to twelve risk groups,

defined by the pre-SRT PSA classes < 0.1, 0.1-0.2, 0.2-0.4, and > 0.4 ng/mL and the GS, ≤ 6 vs. 7 vs. ≥ 8 [656].

In one report on 464 SRT patients receiving median 66.6 (max. 72) Gy, acute Grade 2 toxicity was recorded in 4.7% for both the GI and GU tract. Two men had late Grade 3 reactions of the GI tract. Severe GU tract toxicity was not observed. Late Grade 2 complications occurred in 4.7% (GI tract) and 4.1% (GU tract), respectively, and 4.5% of the patients developed moderate urethral stricture [636]. In a retrospective cohort of 285 men receiving 3D-CRT (38%) or IMRT (62%) with 66 Gy in 95% of cases, the high-dose subgroup did not show a significant increase in toxicity [657].

In a RCT on dose escalation for SRT involving 350 patients, acute Grade 2 and 3 GU toxicity was observed in 13.0% and 0.6%, respectively, with 64 Gy and in 16.6% and 1.7%, respectively, with 70 Gy. Gastrointestinal tract toxicity of Grades 2 and 3 occurred in 16.0% and 0.6%, respectively, with 64 Gy, and in 15.4% and 2.3%, respectively, with 70 Gy. Late effects are yet to be reported [658].

With dose escalation over 72 Gy and/or up to a median of 76 Gy, the rate of severe side-effects, especially GU, clearly increases, even with newer planning and treatment techniques [659,660]. Of note, when compared with 3D-CRT, IMRT was associated with a reduction in Grade 2 GI toxicity from 10.2 to 1.9% (p=0.02), but had no differential effect on the relatively high level of GU toxicity (5-yr: 3D-CRT 15.8% vs. IMRT 16.8%) [659]. After a median salvage IMRT dose of 76 Gy, the five-year risk of Grade 2-3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [660].

6.3.5.1.2.Comparison of adjuvant radiotherapy (ART) and salvage radiotherapy (SRT)

The largest retrospective case-matching study to evaluate ART vs. early SRT included pT3N0 R0/R1 patients only (ADT was excluded), in which 390 out of 500 observation-plus-early-SRT patients (median pre-SRT PSA was 0.2 ng/mL) were propensity matched with 390 ART patients. Two and five years after surgery, biochemically no evidence of disease (bNED) rates were 91% and 78% for ART vs. 93% and 82% after salvage RT, respectively. Subgroup analyses did not yield significant differences for the two approaches. It was concluded that early salvage RT does not impair PCa control, but clearly helps to reduce over-treatment, which is a major issue in both ART and in SRT [661].

The results were confirmed for metastasis-free and OS [654]. However, these retrospective studies are underpowered for high-risk cases such as pT3b/R1/GS 8-10.

Both approaches (ART and SRT) together with the efficacy of neoadjuvant ADT are currently being compared in three prospective RCTs: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) in the United Kingdom, the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES), and Groupe d'Etude des Tumeurs Uro-Génitales (GETUG 17).

Decision-making on whether to proceed with adjuvant RT, for high-risk PCa, pT3-4 pN0 M0 with undetectable PSA after RP, or to postpone RT as an early salvage

procedure in the event of biochemical relapse, remains difficult. In everyday practice, the urologist should explain to the patient before RP that adjuvant RT may be of benefit if the patient has negative prognostic risk factors. Ultimately, the decision on whether to treat requires a multidisciplinary approach that takes into account the optimal timing of RT when it is used, and provides justification when it is not, will best inform the discussion between the physician and the patient.

6.3.5.2.Management of PSA failures after radiation therapy

Therapeutic options in these patients are ADT or local procedures such as salvage RP (SRP), cryotherapy, interstitial brachytherapy and HIFU [662-671]. Strong recommendations regarding the choice of any of these techniques cannot be made as the available evidence for these treatment options is of low quality. The following is an overview of the most important findings regarding each of these techniques with a proposal for their indications.

6.3.5.2.1.Salvage radical prostatectomy

Salvage RP after RT has the longest history and best likelihood of local control relative to other salvage treatments. However, this must be weighed against the possible adverse events, which are increased compared to primary surgery because of the risk of fibrosis and poor wound healing due to radiation.

6.3.5.2.1.1.Oncological outcomes

In a recent SR of the literature, Chade, et al. showed that SRP gave five- and ten-year BCR-free survival estimates ranging from 47-82% and from 28-53%, respectively. The ten-year CSS and OS rates ranged from 70-83% and from 54-89%, respectively. The pre-SRP PSA value and prostate biopsy GS were the strongest predictors of the presence of organ-confined disease, progression, and CSS [672].

In most contemporary series, organ-confined disease, negative surgical margins, and the absence of seminal vesicle and/or LN metastases were favourable prognostic indicators associated with a better DFS of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa [671].

6.3.5.2.1.2.Morbidity

Compared to primary open RP, SRP is associated with a higher risk of later anastomotic stricture (47 vs. 5.8%), urinary retention (25.3% vs. 3.5%), urinary fistula (4.1% vs. 0.06%), abscess (3.2% vs. 0.7%) and rectal injury (9.2 vs. 0.6%) [677]. In more recent series, these complications appear to be less common [669,672]. Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients [672].

6.3.5.2.1.3.Summary of salvage radical prostatectomy

In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least ten years, a pre-SRP PSA < 10 ng/mL and biopsy GS ≤ 7, no LN involvement or evidence of distant metastatic disease pre-SRP, and who's initial clinical staging was T1 or T2 [672]. A meta-regression analysis suggested that SRP

may be associated with worse continence outcomes than non-surgical approaches [679].

6.3.5.2.2.Salvage cryoablation of the prostate

6.3.5.2.2.1.Oncological outcomes

Salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP, as it has a potentially lower risk of morbidity and equal efficacy. However, the very few studies available have shown disappointing results. In a review of the use of SCAP for recurrent cancer after RT, the five-year BDFS estimates ranged from 50-70%. A durable response can be achieved in ~50% of patients with a pre-SCAP PSA < 10 ng/mL [680]. In a multicentre study reporting the current outcome of SCAP in 279 patients, the five-year BCR-free survival estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15/46 patients (32.6%) who underwent prostate biopsy after SCAP [681].

A case-matched control study comparing SRP and SCAP was performed in men with recurrent PCa after RT. The authors compared the oncological outcomes of the two salvage treatment options after mean follow-up periods of 7.8 (SRP group) and 5.5 years (SCAP group). The five-year BCR-free survival was 61% following SRP, significantly better than the 21% detected after SCAP. The five-year OS was also significantly higher in the SRP group (95% vs. 85%) [682].

6.3.5.2.2.2.Morbidity

According to Cespedes, et al. [686], the risks of urinary incontinence and ED at at least twelve months after SCAP were as high as 28% and 90%, respectively. In addition, 8-40% of patients reported persistent rectal pain, and an additional 4% of patients underwent surgical procedures for the management of treatment-associated complications. In a recent study by Pisters, et al., the urinary incontinence rate was 4.4%. The rectal fistulae rate was 1.2% and 3.2% of patients required a TURP for removal of sloughed tissue [681]. With the use of third-generation technology, complications such as urinary incontinence and obstruction/retention have significantly decreased during the last decade (see Table 6.3.5) [687].

6.3.5.2.2.3.Summary of salvage cryoablation of the prostate

In general, SCAP should be considered only for patients with low comorbidity, a life expectancy of at least ten years, an initial organ-confined PCa cT1c to cT2, initial GS ≤ 7, a pre-salvage PSA-DT ≥ sixteen months and a pre-salvage PSA < 10 ng/mL.

6.3.5.2.3.Salvage brachytherapy for radiotherapy failure

Although there is no role for salvage EBRT following local recurrence after previous definitive RT, for carefully selected patients with primary localised PCa and histologically proven local recurrence, HDR- or LDR brachytherapy remain effective treatment options with an acceptable toxicity profile [690-692]. However, the published series are relatively small and consequently this treatment should be offered in experienced centres only. Fifty-two patients were treated at the Scripps Clinic with HDR brachytherapy over a period of nine years [690]. With a median follow-up of 60

months the five-year biochemical control was 51% and only 2% Grade 3 GU toxicities were reported. Comparable with these data, 42 patients were treated in a phase-II-trial at MSKCC in New York [693]. Of note, the median pre-treatment dose was 81 Gy given with IMRT and the prescription HDR-dose of 32 Gy was delivered in four fractions over 30 hours. The biochemical relapse-free survival after five years was 69% (median follow-up 36 months). Grade 2 late side-effects were seen in 15% and one patient developed Grade 3 incontinence. However, older data with higher rates of side-effects have been reported [694].

Using LDR brachytherapy with 103palladium, long-term outcome was reported in 37 patients with a median follow-up of 86 months [691]. The biochemical control rate after ten years was 54%. However, the crude rate of ≥ Grade 2 toxicity was 46% and ≥ Grade 3 toxicity was 11%. These side-effects were comparable with a series of 31 patients treated with salvage I-125 brachytherapy in the Netherlands. Therefore, in these small series, late side-effects seem to be lower with HDR brachytherapy [695]. In conclusion, freedom from BCR after salvage HDR- and LDR brachytherapy is promising and the rate of severe side-effects in experienced centres seem to be acceptable. Salvage brachytherapy remains a treatment option for selected patients with histologically proven local recurrence after RT.

6.3.5.2.4.Salvage high-intensity focused ultrasound

6.3.5.2.4.1.Oncological outcomes

Salvage HIFU has more recently emerged as an alternative thermal ablation option for radiation-recurrent PCa. Most of the data were generated by one high-volume centre. Median follow-up was very short, and outcome measures were non-standardised.

6.3.5.2.4.2.Morbidity

Again, most of the data were generated by one high-volume HIFU centre. Important complication rates were mentioned and are at least comparable to other salvage treatment options.

6.3.5.2.4.3.Summary of salvage high-intensity focused ultrasound

There is a lack of data which prohibits any recommendation regarding the indications for salvage HIFU.

6.3.6.Salvage lymph node dissection

Novel imaging modalities improve the early detection of nodal metastases [702]. The surgical management of (recurrent) nodal metastases in the pelvis has been the topic of several retrospective analyses [410,702,703]. The majority of treated patients showed BCR but clinical recurrence-free and CSS ten-year survival over 70% has been reported [410,704]. Neither the template nor the real value of nodal salvage dissection is available. It must, however, be remembered that the imaging modalities under-evaluate the real nodal involvement. Biochemical recurrence rates were found to be dependent on PSA at surgery and location and number of positive nodes [705]. Addition of RT to the lymphatic template after salvage LND may improve the BCR

rate [706]. The real efficacy of this salvage procedure remains unproven, as is its impact on survival [707].

6.3.7.Hormonal therapy

The Guidelines Panel conducted a SR including studies published from 2000 onwards [708]. The key findings are summarised below:

Conflicting results on the clinical effectiveness of HT after previous curative therapy of the primary tumour were found. Some studies reported a favourable effect of HT, including the only RCT addressing the research question of this review (86% vs. 79% advantage in OS in the early HT group) [709]. Other studies did not find any differences between early vs. delayed, or no, HT. One study found an unfavourable effect of HT [710]. This may be the result of selecting clinically unfavourable cases for (early) HT and more intensive diagnostic work-up and follow-up in these patients.

The studied population is highly heterogeneous regarding their tumour biology and therefore clinical course. The following factors were found predictive for poor outcomes; CRPC, distant metastases (DM), CSS, OS, short PSA-DT, high GS, high PSA, increased age and comorbidities. In some studies, such as the Boorjian, et al. study [587], high-risk patients, mainly defined by a high GS and a short PSA-DT (most often less than six months), seem to benefit most from (early) HT, especially in men with a long life expectancy.

No data were found on the effectiveness of different types of HT, although it is unlikely that this will have a significant impact on survival outcomes in this setting. Non-steroidal anti-androgens have been claimed to be inferior compared to castration, but this difference was not seen in M0 patients [594]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [711]. A small advantage was found in some QoL domains but not overall QoL outcomes. An important limitation of this RCT is the lack of any stratifying criteria such as PSA-DT or initial risk factors.

Based on the lack of definitive efficacy and the undoubtedly associated significant side-effects, patients with recurrence after primary curative therapy should not receive standard HT. Only a minority of them will progress to metastases or PCa-caused death. The objective of HT should be to improve OS, postpone DM, and improve QoL. Biochemical response to only HT holds no clinical benefit for a patient. For older patients and those with comorbidities, the side-effects of HT may even decrease life expectancy; in particular, cardiovascular risk factors need to be considered [712,713]. Early HT should be reserved for those at highest risk of disease progression, defined mainly by a short PSA-DT at relapse (less than six to twelve months) or a high initial GS (> 7), and a long life expectancy.

6.3.8.Observation

Observation until the development of clinically evident metastatic disease may represent a viable option for patients with low-risk features (PSA-DT > 12 months, time to BCR > 3 years, GS ≤ 7 and stage ≤ T3a) or unfit patients with a life expectancy less than ten years and/or are unwilling to undergo salvage treatment. In

unselected relapsing patients, the median actuarial time to the development of metastasis will be eight years and the median time from metastasis to death will be a further five years [569].

6.3.9.Guidelines for second-line therapy after treatment with curative intent

Local salvage treatment	Strength rating
Recommendations for biochemical recurrence after radical prostatectomy	
Offer active surveillance and possibly delayed salvage radiotherapy (SRT) to patients with biochemical recurrence and favourable prognostic factors (≤ pT3a, time to biochemical recurrence > three year, prostate-specific antigen doubling-time (PSA-DT) > twelve months, Gleason score ≤ 7), who may not benefit from intervention.	Strong
Treat patients with a PSA rise from the undetectable range with SRT. The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	Strong
Recommendations for biochemical recurrence after radiotherapy	
Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage radical prostatectomy (SRP).	Weak
Salvage RP should only be performed in experienced centres.	Strong
Do not offer high intensity focused ultrasound, cryosurgical ablation and salvage brachytherapy to patients with proven local recurrence since it is still experimental.	Strong
Recommendations for systemic salvage treatment	
Do not offer androgen deprivation therapy to M0 patients with a PSA-DT > twelve months.	Strong

7.1.Follow-up: After local treatment

7.1.1.Definition

Local treatment is defined as RP or RT, either by EBRT or LDR- or HDR-brachytherapy, or any combination of these. Unestablished alternative treatments, such as HIFU and cryosurgery do not have a well-defined, validated PSA cut-off to define BCF, but follow the general principles as presented in this section.

7.1.2.Why follow-up?

Recurrence occurs after primary therapy in many patients who have previously received treatment with intent to cure.

Patients who receive curative therapy are followed up to discuss the need and possibility of second-line treatment either with curative or palliative intent. It will be based on initial treatment, patient age, comorbidity and the patient's own wishes.

7.1.3.How to follow-up?

The procedures indicated at follow-up visits vary according to clinical situation. The examinations discussed below are routinely used to detect PCa progression or residual disease. Prostate specific antigen level and DRE are the only tests that should be performed routinely. A disease-specific history is mandatory at every follow-up visit and includes psychological aspects, signs of disease progression, and treatment-related complications. Evaluation of treatment-related complications must be individualised, which is beyond the scope of these Guidelines. The examinations used for cancer-related follow-up after curative surgery or RT are discussed below.

7.1.3.1.Prostate-specific antigen monitoring

Measurement of PSA is a cornerstone in follow-up after local treatment. Expectations differ after RP and RT, but PSA recurrence often precedes clinical recurrence [585,808]. A single, elevated, serum PSA level should be confirmed before starting second-line therapy based solely on PSA elevation.

7.1.3.2.Definition of prostate-specific antigen progression

The PSA level for definition of treatment failure differs between RP and RT. No formal consensus exists regarding the best definition of PSA relapse after RP. Recurrent cancer after RP is usually defined by two consecutive PSA rises $\geq$ 0.2 ng/mL [809]. However, others have argued for a higher cut-off of 0.4 ng/mL to best represent the risk of subsequent metastases (see Section 6.3.2) [585].

Ultrasensitive PSA assay remains controversial for routine follow-up after RP. Men with an ultrasensitive PSA nadir < 0.01 ng/mL have a 4% likelihood of early biochemical relapse [810]. Detectable post-operative ultrasensitive PSA does not predict BCR in all cases, although it adds prognostic value. In men with ultrasensitive PSA > 0.05 ng/mL, 66.8% remained free of biochemical disease at five years [811]. If

survival is improved by early adjuvant treatment after RP (before PSA reaches > 0.2 ng/mL), lower PSA nadir levels may help identify suitable candidates, as well as low PSADT calculated using the first detectable PSA up to 0.2 ng/mL [592].

At the 2006 RTOG-ASTRO Consensus Conference, a new definition of radiation failure was proposed to establish better correlation between definition and clinical outcome, namely, an increase of 2 ng/mL above the post-treatment PSA nadir [586]. It applies to patients with or without HT.

After HIFU or cryotherapy, no endpoints have been validated to indicate clinical progression or survival; therefore, it is not possible to give a firm recommendation of BCF after these alternative local treatments.

7.1.3.3.Prostate-specific antigen monitoring after radical prostatectomy

Prostate-specific antigen is expected to be undetectable within six weeks after successful RP [812]. Persistently elevated PSA in patients treated with RP is thought to be due to residual cancer, either micrometastases or residual pelvic disease.

A rapidly increasing PSA level suggests distant metastases, whereas a later, slowly increasing, level most likely suggests local recurrence. Time to PSA recurrence and tumour differentiation are important predictive factors distinguishing local and systemic recurrence [813]. Local treatment failure and distant metastases can occur with undetectable PSA levels. This is rare and occurs mostly in patients with undifferentiated tumours [814]. Thus, in patients with favourable pathology (< pT3, pN0, GS < 8), PSA measurement and disease-specific history could be a single test in follow-up after RP.

7.1.3.4.Prostate-specific antigen monitoring after radiotherapy

Prostate-specific antigen level falls slowly after RT compared with RP. A nadir < 0.5 ng/mL is associated with a favourable outcome after RT [815], although the optimal value is controversial. The interval before reaching the nadir can be up to three years or more. After RT, PSA-DT is correlated with site of recurrence; patients with local recurrence have a PSA-DT of thirteen months compared to three months for those with distant failure [816].

7.1.3.5.Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level [814]. However, this has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. Prostate-specific antigen measurement and DRE comprise the most useful combination for first-line examination in follow-up after RT or RP, but PSA measurement may be the only test needed in cases with favourable pathology (< pT3, pN0, Gleason < 8) after RP [817].

7.1.3.6.Transrectal ultrasound, bone scintigraphy, computed tomography, magnetic resonance imaging, and 11C-choline positron emission tomography computed tomography

Imaging techniques have no place in routine follow-up of localised PCa. They are only justified in patients for whom the findings affect treatment decisions, either with BCF or in patients with symptoms. (See Section 6.3.4.2.1 for a more detailed discussion).

7.1.3.6.1.Transrectal ultrasonography/magnetic resonance imaging guided biopsy.

Biopsy of the prostate bed and urethrovesical anastomosis or of the remaining prostate after radiotherapy, are only indicated if local recurrence affects treatment decisions.

7.1.4.When to follow-up?

Most patients who fail treatment for PCa do so early, even if failure only becomes clinically obvious after years. Patients should be followed up more closely during the initial post-treatment period when risk of failure is highest. Prostate-specific antigen measurement, disease-specific history and DRE are recommended at three, six and twelve months post-operatively, every six months thereafter until three years, and then annually.

The first post-treatment clinic visit mainly focusses on detecting treatment-related complications and assist patients in coping with their new situation. Tumour or patient characteristics may allow alterations to this schedule. Patients with poorly differentiated and locally advanced tumours or with positive margins may be followed-up more closely than those with a well-differentiated, intracapsular or specimen-confined tumour. Advanced age or associated comorbidity may make further follow-up in asymptomatic patients superfluous.

7.1.5.Summary of evidence and guidelines for follow-up after treatment with curative intent

Summary of evidence	LE
After radical prostatectomy serum prostate-specific antigen (PSA) level > 0.2 ng/mL is associated with residual or recurrent disease.	2a
After radiotherapy, an increase in PSA > 2 ng/mL above the nadir, rather than a specific threshold value, is the most reliable sign of recurrence.	2a
Palpable nodules and increasing serum PSA are signs of local recurrence.	2a

Recommendations	Strength rating
Routinely follow-up asymptomatic patients, by obtaining a disease-specific history and serum prostate-specific antigen (PSA) measurement. These should be performed at three, six and twelve months after treatment, then every six months until three years, and then annually.	Strong
During follow up, perform a systematic DRE after surgery if unfavourable pathology (> pT3, pN1, Gleason ≥ 8).	Weak
During follow up, perform a systematic DRE after radiotherapy.	Strong
At recurrence, only image to detect local recurrence if it affects treatment planning.	Strong
Do not routinely offer bone scans and other imaging modalities to asymptomatic patients if there are no signs of biochemical relapse. In case patients have bone pain or other symptoms of possible progression, restaging should be considered irrespective of serum PSA level.	Strong