Follow-up After Radical Treatments and Relapse

17

Nicolas Mottet

Contents

N. Mottet, M.D., Ph.D.
Urology department, University hospital,
CHU St Etienne, 42055 St Etienne Cedex 2, France
e-mail: nicolas.mottet@chu-st-etienne.fr

Whatever the curative treatment modality, failure is not uncommon. Curative treatment is defined as radical prostatectomy or radiotherapy (either external or interstitial) alone, or in combination. We will also cover the nonfully established procedures, such as HIFU or cryotherapy. Between 27% and 53% of all patients undergoing a "curative treatment" will develop local or distant recurrences within 10 years of initial therapy, and 16–35% of patients will receive second-line treatment within 5 years of initial therapy (Lu-Yao et al. 1996; Grossfeld et al. 1998). Some failures might have an impact on patient's survival, leading to second-line treatments with curative intent again or to palliation, sometimes for years. The balance between second-line treatment side effects and the expected benefits must always be considered. The primary aim of a follow-up policy is to find a situation before advanced disease is present in order to be curative again or as effective as possible in term of palliation. Usually, this is based on an early diagnosis.

17.1 How to Follow-up?

Only PSA level, and eventually DRE, needs to be carried out routinely. During each visit, a disease-specific history is mandatory including signs of disease progression and treatment-related complications (beyond the scope of this chapter).

DRE is performed to follow the gland and assess whether or not there is a suspicion of local recurrence. After radiotherapy, the DRE findings

M. Bolla, H. van Poppel (eds.), *Management of Prostate Cancer*,
DOI 10.1007/978-3-642-27597-5_17,

are usually difficult to interpret. A newly detected nodule should be considered as suspicious. Although discussed a local recurrence is possible without any PSA rise (Oefelein et al. 1995; Leibman et al. 1995). But this has only been proven in patients with undifferentiated tumors. The measurement of PSA level is the cornerstone in the follow-up strategy. PSA recurrence nearly always precedes clinical recurrence, in some cases by many years (Horwitz et al. 2005; Stephenson et al. 2006). Usually, a single PSA suggesting a recurrence must be confirmed by another measurement.

Thus, PSA measurement and DRE comprise the most useful combination of tests as first-line examination in follow-up after radiotherapy or radical prostatectomy, but PSA measurement may well be the only test in cases with favorable pathology (Chaplin et al. 2005).

Other modalities such as transrectal sonography, bone scan, computed tomography, or MRI have no place in asymptomatic men. In new developing bone symptoms, a bone scan is mandatory as metastatic disease may occur even at undetectable PSA level (Oefelein et al. 1995; Leibman et al. 1995).

17.2 When to Follow-up?

Most recurrence occurs during the first 2 or 3 years. A closer follow-up is therefore useful during the first 3 years, with a proposed interval of 3, 6, and 12 months initially, every 6 months for 2 years thereafter, followed by a yearly interval later on (Mottet et al. 2011). This regimen must be adapted based on tumor and patient characteristics: nodal disease, positive margins, or Gleason > 8 might shorten the intervals, while advanced age or significant comorbidities might expend the intervals.

17.3 PSA Definition of Recurrence

The level of PSA at which to define treatment failure differs between treatment modalities. If a consensus exists regarding surgery or radiotherapy, none exists for HIFU or cryotherapy. The PSA recurrence is defined based on the PSA nadir after treatment.

After surgery, PSA is expected to be undetectable (i.e., <0.1 ng/ml) within 6 weeks after the procedure (Stamey et al. 1889). After radiotherapy (external beam or brachytherapy), the time to nadir is prolonged, sometimes as long as 3 years. The optimal value remain controversial, a nadir below 0.5 ng/ml being possibly associated with a better outcome (Ray et al. 2006).

Recurrence following surgery is usually defined by two consecutive values of 0.2 ng/ml increasing (Boccon-Gibod et al. 2004; Mottet et al. 2011). Other authors have argued for an even higher cut-off of 0.4 ng/ml (Scher et al. 2004) as this threshold was the best predictor of secondary metastases (Stephenson et al. 2006). A single PSA value above a threshold is inappropriate: only 49% of patients had a second PSA increase if above 0.2 ng/ml, compared to 62% and 72% if above 0.3 or 0.4 ng/ml, respectively (Amling et al. 2001). So far, the use of an ultrasensitive PSA assay is not justified for routine follow-up (Taylor et al. 2006); also, preliminary results suggest that this might change in the future (Hong et al. 2010). Values between the nadir and the defined threshold are controversial in term of prognosis significance.

Following radiation therapy, the previous ASTRO definition of relapse was three consecutive increases (ASTRO 1997). The new ASTRO-RTOG definition of failure (also known as the Phoenix definition) is a rise of 2 ng/ml above the PSA nadir (Roach et al. 2006). It is valid for patients treated with radiotherapy alone or combined with hormonotherapy.

After HIFU or cryotherapy, a variety of definitions for PSA relapse have been used (Aus 2006), with a cut-off around 1 ng/ml. No accepted definition is available, as none have been validated against clinical progression or survival.

17.4 PSA Relapse and Survival

Nowadays, PSA relapse by itself is not a surrogate marker for survival. And only recently was the relation between PSA relapse and survival observed. In a retrospective analysis of 3,071

Table 17.1 Prostate-cancer-specific mortality based on PSA-DT at relapse (D'Amico et al. 2003)

		PSA-DT < 12 months (%)	PSA-DT < 6 months (%)	PSA-DT < 3 months (%)
Surgery	Year 5	7.6	13.9	31.2
	Year 10	17.5	34.1	67.8
Radiotherapy	Year 5	15.9	27	38.4
	Year 10	39.6	60.6	76.6

Table 17.2 Major findings to discriminate between a probable local or systemic relapse after a local treatment

	Relapse definition (PSA based)	Favoring local relapse	Favoring systemic relapse
After surgery	PSA > 0.2 ng/ml and increasing	pN0, ≤pT3a	Postoperative detectable PSA (>0.1 ng/ml) and Gleason > 7
		Delay to recurrence >2 years (discussed)	pN1, pT3b
		PSA-DT at relapse >12 months	PSA-DT (relapse) <6 months
		Other possible parameters: Gleason ≤ 6, positive margins	Other possible parameters: Gleason > 7
After radiotherapy	PSA > nadir + 2 ng/ml	PSA nadir <0.5 ng/ml	PSA at 1 year >2 ng/ml
		PSA at 1 year <2 ng/ml	PSA-DT at relapse <6 months
		PSA-DT at relapse >12 months	

men treated with surgery, biochemical relapse occurred after a median 7.4 years in 546 men. In a multivariate analysis, PSA failure was associated with overall survival (hazard ratio 1.03, $p=0.025$) (Choueiri et al. 2010). Similar results regarding prostate-specific survival have also been observed in another retrospective cohort of 1,270 men after either surgery or radiotherapy (Uchio et al. 2010).

PSA-relapsing patients represent a heterogeneous cohort of patients. The PSA evolution is one of the most important prognostic parameter. In 2003, based on 5,918 patients with surgery and 27,851 with external beam treatment, D'Amico demonstrated a direct relationship between the PSA-doubling time (PSA-DT) and the specific mortality (Table 17.1). A PSA-DT below 3 months was associated with specific mortality (hazard ratio 19.6 [12.5–30.9]) (D'Amico et al. 2003).

17.5 Relapse: Local or Systemic?

To determine whether the recurrence is local or systemic is of paramount importance and will change the treatment modality. About 50% of patients after surgery will have a local failure (ASTRO 1997). Major findings are summarized in Table 17.2.

17.5.1 Surgery

A persistently elevated PSA (i.e., >0.1 ng/ml) equals persistence of prostatic tissue. This is generally thought to be residual cancer due to either micrometastases that were not detected or undetectable beforehand, or residual disease in the pelvis possibly due to positive surgical margins. The benign origin of this PSA is unlikely. The prognosis of these patients is worse compared to those with an undetectable PSA, but again is inhomogeneous: PSA nadir, margin status, and specimen Gleason score are independent predictors for recurrence, while PSA nadir and pT3b predict overall mortality (Moreira et al. 2009).

In patients with an undetectable PSA, its evolution is the key factor. A high PSA velocity (above 0.75 ng/ml/year) or a low PSA-DT are strong predictors of systemic relapses (threshold mainly <6 months) (Pound et al. 1999; Roberts et al. 2001; Rosenbaum et al. 2004; Freedland

et al. 2007), or specific survival (threshold <3 or 12 months) (Albertsen et al. 2004; Zhou et al. 2005). For some authors, this parameter is the only predictor for systemic relapse in multivariate analysis including Gleason and recurrence delay. To obtain a reliable value for the PDA-DT, at least three values above 0.1 ng/ml are mandatory (Svatek et al. 2006). The MSKCC website might also be helpful (http://nomograms.mskcc.org/prostate/PsaDoublingTime.aspx).

Clinical parameters have also been suggested to predict local or systemic recurrence, such as pT status (pT3b, pN1, Gleason ≥ 7) being associated with an increased risk of systemic relapse (Pound et al. 1999). The margin status is not a predictive factor for the type of relapse (Pound et al. 1999). The time to PSA recurrence is more controversial. Initially considered as a predictive factor of systemic relapse if less than 2 years, this finding has been recently discussed in a retrospective cohort of 14,632 patients followed for a median 11.5 years after surgery (Boorjian et al. 2011).

17.5.2 Radiation Therapy

Achieving a PSA nadir of less than 0.5 ng/ml seems to be associated with a favorable outcome (Ray 2006). The PSA at 1 year after radiotherapy alone is also proposed as a predictor of metastasis and death if above 2 ng/ml (Alcantara et al. 2007). As after surgery, a low PSA-DT is associated with secondary metastases (Maffezzini et al. 2007) with less clear thresholds: <3 months, 6 months, or 12 months (Zelefsky et al. 2005; D'Amico et al. 2006).

17.6 Clinical Workout at Relapse (Table 17.3)

Table 17.3 Proposed workout in PSA-relapsing patients

Bone scintigraphy and *CT scans*: no additional diagnostic value unless PSA above 20 ng/ml or PSA velocity above 2 ng/ml/year
MRI after surgery has no place in routine practice. After radiotherapy, if a local salvage curative treatment is considered, biopsies and endorectal MRI should be considered. 11C-PET might play a role in the future, for PSA above 1–2 ng/ml

17.6.1 Biopsies

They have no place after surgery as the results of salvage radiotherapy did not differ based on the biopsy results (Koppie et al. 2001; Leventis et al. 2001). They might be considered after radiotherapy in some cases.

17.6.2 Images

Bone scan and abdominal CT scan might be safely omitted in the routine workup of relapsing patients based on their low sensitivity and specificity (Scher et al. 2004). Only 4.1% and 27% of the bone scan were positive out of 144 scans in 93 patients (Cher et al. 1998); the lowest PSA associated with positive findings was 46 ng/ml in the absence of adjuvant hormonal therapy, and 15.47 ng/ml in patients who had received hormonal therapy. The likelihood of a positive bone scan remains ≤5% as long as PSA remains below 40 ng/ml. Similar data have been achieved by another (Gomez et al. 2004), the PSA predicting the finding on bone scan, while the PSA velocity predicted the finding of bone and CT scan. Recently, 239 relapsing patients were analyzed regarding the probability of having a positive bone scan after surgery (Dotan et al. 2005). Based on 60 positive scans, 4%, 36%, 50%, and 79% had a positive scan for a PSA level of respectively 0–10, 10–20, 20–50, or above 50 ng/ml. In multivariate analysis, PSA slope, PSA velocity, and total PSA were predictors of positive scan, total PSA being the highest predictive factor.

Endorectal MRI has been considered as a useful technique after surgery (D'Amico AV et al. 2006). In a cohort of 48 patients, its sensitivity was as high as 81%, with the mean PSA of 2 ng/ml at the time of diagnosis. Another series of

72 men obtained the following results (Cirillo et al. 2009): Sensitivity, specificity, predictive positive value, negative predictive value, and accuracy were respectively 61.4%, 82.1%, 84.4%, 57.5%, and 69.4% for unenhanced endorectal MRI and 84.1%, 89.3%, 92.5%, 78.1%, and 86.1% for enhanced endorectal MRI, with a statistical difference favoring the enhanced MRI. The mean total PSA was 1.23% ± 1.3 ng/ml. In practice, relapse after surgery is considered for PSA levels below 0.5 ng/ml where endorectal MRI is still too insensitive and inaccurate. Therefore, endorectal MRI has no place in routine practice for relapses after surgery.

Positron emission tomography (PET) published data suggest that this modality might be useful in relapsing patients. Only PET choline must be considered, and it must be remembered that the uptake of 11C-choline is not specific for prostate cancer. Its overall detection rate varies between 38% and 98% (Picchio et al. 2011). There is a link between the positive rate and the PSA level: if below 1 ng/ml, the detection rate is inacceptable (5–36%), a cut-off value of 1.4 ng/ml being considered as the lowest acceptable value (Giovacchini et al. 2010a) and others considering 2–2.4 ng/ml as optimal (Castellucci et al. 2009). Apart from PSA level, there is also a link between the PSA-DT and the positivity rate (Castellucci et al. 2009; Giovacchini et al. 2010b), suggesting that for PSA-DT <3 months, this imaging modality might have a place. Immunoscintigraphy using Prostacint (a radiolabelled monoclonal antibody based on prostate-specific membrane antigen for messenger RNA (PSMA), known as 111-indium capromab pendetide) has no role, based on high false-positive and negative rates (Scher et al. 2004).

17.6.3 PSA Relapse Following Radiation Therapy: Local Staging

This local staging plays a major role if a local salvage procedure is considered. According to an ASTRO consensus recommendation (Cox et al. 1999), systematic prostate biopsy at PSA relapse has no place. But when considering a local salvage treatment, especially radical prostatectomy, they have a major role (Heidenreich et al. 2008). They are best performed after 1.5–2 years following radiation therapy or brachytherapy seeds and 3 months after cryotherapy or high-intensity focused ultrasound (HIFU): a local relapse is confirmed if positive (viable cancer cells) beyond 2 years after radiation therapy. In those situations, endorectal MRI, MRI spectroscopy, and dynamic contrast-enhanced MRI might have a major role (Rouvière et al. 2004; Pucar et al. 2005; Sala et al. 2006) based on a clear differentiation of active and fibrous tissue on T2-weighted signal, with a sensitivity and a specificity of 86% and 96%, respectively, for extracapsular extension and seminal vesicle invasion. They appear to be more sensitive than TRUS or TRUS-guided prostate biopsies to detect viable tumor.

17.7 Treatment of Biochemical Failure After Treatment with Curative Intent

The timing and treatment modality of PSA-only recurrence remain controversial. The decision to undergo a salvage treatment must be evidence-based with answers on several parameters: what is the patient's expected survival, what is the natural history of his recurrence, is it a local or a systemic one, and what is to be expected from the treatment: overall survival benefit, symptom benefit, symptom-free duration benefit, and at which side-effects cost?

17.7.1 Evaluation of the Expected Survival

This point is the cornerstone of any decision. A patient with a local relapse and a 3-year PSA-DT will be offered different modalities: if he is 55 years old, ECOG 0, or 78 years old, ECOG 3. Above 70 years of age, the expected

survival is really heterogeneous as shown by Walter et al. (2001). A 14-year life expectancy is expected at 75 years of age if healthy (25% of the population), 9 years if vulnerable, while it is only 5 years if frail (25% of the population). This highlights the importance of an individual evaluation. Many tools are available, none being perfect and really simple, the ASA, ECOG, or Karnovsky being too vague to really discriminate. The most often used is the Charlson, and the most predictive and simple might be the chronic disease score (CDS) (Boulos et al. 2006), or even simpler such as the gait speed (Studenski et al. 2011). For older patients, guidelines are available (Droz et al. 2010). A detailed analysis of these tools is far beyond the scope of this article, but considering this point before any decision is all the more important since the patient is having comorbidities. They will lead the survival in the vast majority of the situations (Lu-Yao et al. 2011).

17.7.2 Natural History After Relapse

The overall median time from recurrence to metastasis is 8 and 5 years from metastasis to death (Pound et al. 1999). Different results have been published regarding long-term metastasis-free survival or specific survival in relapsing patients after surgery. At 15 years, Pound et al. (1999) reported a 25% metastases-free survival, while Boorjian et al. (2011) observed a 76% metastases-free survival. The same discrepancy was observed regarding 15-year specific survival: from 53% (Freedland et al. 2006) to 84% (Boorjian et al. 2011). Not surprisingly, major factors associated with survival were those previously discussed: low PSA-DT, high Gleason score, pN+, or pT3b status. The differences in the long-term survival reported might be associated with different populations, different adjuvant, or salvage policies (early or symptom differed). However, these results highlight the fact that apart from very aggressive situations (Gleason > 7, pN+, pT3b, PSA-DT < 6 months at relapse), the clinical impact of relapse is usually differed to a very long term. This might question the systematic use of salvage treatment with these associated side effects (Pinover et al. 2003; Guillonneau and Fizazi 2011).

17.8 Salvage After Surgery

17.8.1 Salvage Radiation Therapy

The place of adjuvant or salvage radiotherapy is discussed elsewhere (Chap. 13, Wiegel). Available data on salvage radiotherapy suggest some points to be clear predictors of efficacy. Clinical stage (pT < pT3b, pN0, Gleason) (Stephenson et al. 2004b) appears to be predictive, while margin status remains controversial (Leventis et al. 2001), the negative status being often considered to increase the risk of a second failure (Katz et al. 2003; Stephenson et al. 2004b). The most powerful factor appears again to be the PSA, either its doubling time or its preradiation status. A normalized postoperative PSA is a strong predictor of efficacy compared to a PSA > 0.1 ng/ml (Cox et al. 1999). A PSA-DT above 10 or 12 months is also associated with a better response to salvage radiotherapy (Leventis et al. 2001; Stephenson et al. 2004b). Finally, the PSA at the time of radiotherapy is the one of the strongest predictor. In a retrospective multicenter cohort of 1,540 patients with a salvage radiotherapy (Stephenson et al. 2007), the 6-year biochemical-free survival was 48% in men with PSA <0.5 ng/ml, whereas it was only 40%, 28%, and 18% in men with PSA levels of respectively 0.51–1 ng/ml, 1.01–1.5 ng/ml, and >1.5 ng/ml, respectively. Even if highest in patients with the lowest PSA, a metastasis-free survival benefit was observed in all PSA categories (<0.2, 0.2–1.0, >1.0 ng/ml), from a subgroup analysis of the SWOG S8974 trial (Swanson et al. 2007). All these parameters have been combined in prediction tools either segmented (Buskirk et al. 2006) or continuous (Stephenson 2007), none being externally validated. The survival impact of this salvage procedure has only recently been observed (Trock et al. 2008). In a retrospective cohort of 635 relapsing patients, with a median follow-up of 6 years after recurrence, the benefit of salvage radiation for prostate-cancer-specific mortality was seen (threefold increase in prostate-cancer-specific survival) if

delivered less than 2 years after relapse. In a multivariate analysis, the benefit however was only seen in those with the most aggressive relapse: in those with a PSA-DT below 6 months, the 10-year specific survival was 82% compared to 30% without salvage radiotherapy, while it was 86% and 75% for those with a PSA-DT above 6 months. No apparent benefit was observed in those with a long PSA-DT. Based on a retrospective study, these results must be externally confirmed, ideally in a prospective trial.

The most frequently used dose for adjuvant and salvage radiation is less than 66 Gy. However, as with primary treatment, an increased dose in the salvage setting may improve the biochemical response (Swanson et al. 2007) without worsening local toxicity (King and Kapp 2008; King and Spiotto 2008). Dosages up to 70 Gy showed better biochemical recurrence-free rates at higher doses, with 66.8 Gy found to be the dose required for 50% biochemical recurrence-free survival (TCD50).

Target volume delineation is another conflicting issue, even if guidelines are available (Poortmans et al. 2007). They have been found to vary by up to 65% between different radiotherapists (Wiltshire et al. 2007; Mitchell et al. 2009). The place of whole pelvis salvage radiation remains unclear, even if suggested to be beneficial in high-risk patients only (Spiotto et al. 2007). In the EORTC 22911 study, 3.1% of men had to interrupt adjuvant radiation because of local complaints, mainly diarrhea. Although grade 3 or 4 toxicity is rare for adjuvant or salvage radiation, it was almost doubled in the adjuvant arm of the EORTC 22911 study (2.6% vs. 4.2%) (Bolla et al. 2005) and the SWOG S8794 (Thompson et al. 2009) study, particularly urethral stricture and incontinence.

17.8.2 Salvage Hormonal Therapy

Compared to salvage radiotherapy, no randomized trial is available using salvage androgen deprivation therapy (ADT), and we must rely on retrospective cohorts only. Two large cohorts are available. In the first one (Moul et al. 2004) including 1,352 patients with postoperative PSA recurrence, no significant difference was observed in the time to clinical metastases with early ADT (at PSA recurrence, using different PSA thresholds) compared to delayed ADT (at the time of clinical metastases) ($p=0.66$). However, early ADT (either when PSA was below 5 or 10 ng/ml) delays the time to clinical metastases in high-risk patients (Gleason >7 and/or a PSA-DT ≤12 months). But ADT had no impact on specific survival. The second large cohort (Siddiqui et al. 2008) is based on 6,401 pN0 patients with postoperative ADT, including 265 with salvage ADT at relapse and a median 10 years of follow-up. Using a matched-paired comparison, no specific survival benefit was observed if salvage was used whatever the considered PSA threshold (0.4, 1, or 2 ng/ml), and even a possible decreased specific survival in some subgroups. Lastly, a highly selected group of 91 relapsing patients were treated with ADT at the time of metastasis (Makarov et al. 2008). In this cohort, the median time from surgery to failure was 24 months, 36 months from failure to metastasis, and 84 months from metastasis to death, representing a median 168 months between surgery to death. PSA-DT below 3 months again was a highly significant predictor of death. Once the salvage ADT is instituted, the obtained PSA nadir is predictive of specific survival, the threshold being a PSA below 0.2 ng/ml, even with a PSA-DT that is below 3 months (Stewart et al. 2005).

All these data have been obtained using a continuous medical castration, mainly surgical or with an LHRH analogue. Results using other medical ADT (nonsteroidal antiandrogen as monotherapy, or minimal androgen blockade) are even more scarce and unreliable.

Intermittent androgen deprivation (IAD) might be an elegant way to overcome the long-term side effects and costs of ADT (Abrahamsson 2010). The trial reported by Tunn et al. (2003) on 218 relapsing patients comparing continuous versus IAD did not show any difference in terms of hormone-refractory status at 48 months. The recently presented SWOG-JPR7 trial (Klotz et al. 2011) in relapsing patients after radiotherapy is a strong plea favoring IAD in relapsing patients, as long as ADT is considered. It will be discussed in the next paragraph.

Compared to the locally advanced situation, the salvage combination of ADT to external beam has been analyzed. No survival benefit was seen in a retrospective cohort (Trock et al. 2008). Last year, the results of the RTOG-9061 trial comparing salvage radiotherapy combined with either placebo or bicalutamide (150 mg daily for 24 months) were reported (Shipley et al. 2011). A benefit in terms of progression-free survival at 7 years (57% compared to 40%, $p < 0.0001$) and metastasis-free survival (92.6% vs. 87.4%, $p = 0.0107$) was observed. But without any overall survival difference, ongoing trials will clarify the effectiveness of such a combination, using more conventional ADT (French GETUG 16) and MRC RADICALS trials. Currently, there is no place for chemotherapy in patients with PSA recurrence only based on available preliminary negative results (Oudard et al. 2011).

17.9 Salvage After Radiotherapy

In a recent review from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) comprising 2,336 patients (Grossfeld et al. 2002) demonstrated that 92% of patients initially irradiated received secondary ADT for PSA progression. In the absence of salvage procedures, the mean time interval from biochemical to clinical progression is approximately 3 years.

Therapeutic options in these patients are ADT or local procedures, such as salvage radical prostatectomy, cryotherapy, and interstitial radiation therapy (Stephenson et al. 2004a; Heidenreich et al. 2010). Salvage surgery has not gained widespread acceptance because of its associated morbidity, namely, incontinence, local recurrences, and rectal injuries. However, in well-selected patients, the procedure may result in long-term disease-free survival.

17.9.1 Salvage Surgery

Salvage radical prostatectomy is a rarely performed procedure based on its poor reputation: difficult procedure with a high associated complication rate, and a poor efficacy. Up to this year, mainly single-center retrospective cohorts were reported. Recently, a large international retrospective cohort of 404 patients has been published (Chade et al. 2011). All had biopsy-proven recurrence; median age was 65 years, and the median presurgery PSA, 4.5 ng/ml (range 0.1–105). None received any form of ADT. After a median 4.4 years of follow-up, the 10-year relapse-free was 37% (31–43%); metastasis-free survival, 77% (71–82%); and specific survival, 83% (76–88%). On multivariate analysis, presalvage PSA, biopsy, and specimen Gleason score predicted relapse-free and metastasis-free survival. Nodal involvement was also predictive of metastasis-free survival. The best outcome was observed with a presalvage PSA below 4 ng/ml and a presalvage biopsy Gleason ≤7. Predictors of organ-confined disease have been clarified (Heidenreich et al. 2010): biopsy Gleason at salvage below 7, less than 50% positive cores at salvage, PSA-DT > 12 months at relapse, and previous brachytherapy.

The toxicity of this difficult procedure is acceptable in tertiary centers with an overall perioperative complication rate ranging from 9% to 27%, a transfusion rate from 4.5% to 29%, a rectal injury from 2% to 3%, and a social continence from 50% to 81% (also, it must be acknowledge that no standard definition has ever been used). The initial radiotherapy modality appears to lead to different preoperative difficulties and postoperative continence results (Heidenreich et al. 2010).

17.9.2 Salvage Brachytherapy

The experience with salvage brachytherapy for radiation failures is very limited (less than 300 cases reported). A systematic review has been recently published (Kimura et al. 2009). Most series are limited (17–49 patients) and have a short follow-up (median 19–64 months). The overall results are at best moderate, with a disease-free survival at 5 years between 34% and 87%. But the use of different failure definition and the unknown use of combined or salvage ADT preclude any clear conclusion. Recently,

Burri reported an extended 86 months median follow-up for 37 patients (Burri et al. 2010), achieving a 10-year biochemical disease-free survival, and CSS were 54% and 96%, respectively. Presalvage PSA below 6 ng/ml was the only associated factor for long-term disease-free survival. Salvage brachytherapy after a combination of external beam and brachytherapy has also been reported with poor results: 20% relapse-free survival at 5 years in 31 patients after 9-year mean follow-up (Moman et al. 2010). All these modalities have been associated with significant grade 3–4 toxicity (GU ranging from 14% to 47%, GI from 6% to 24%).

17.9.3 Salvage High-Intensity Focused Ultrasound (HIFU)

The experience of salvage HIFU after radiation therapy is very limited, based on less than 400 patients reported in retrospective studies (Zacharakis et al. 2008; Murat et al. 2009). Based on the largest series of 167 patients followed for a mean 18 months (Murat et al. 2009), the 3-year relapse-free survival is only 53% (Phoenix definition). The overall oncological control rate after a short median follow-up of near 2 years is in the range of 30–40%. Factors associated with a short relapse-free survival are a high pre-HIFU PSA, a high preradiotherapy D'Amico risk group, and the use of ADT during the treatment. Side effects are significant with 49% incontinence rate (leading to 11% artificial urinary sphincter implantation), 8.5–36% obstruction rate, and 17–20% urethral or bladder neck stricture rate, difficult to manage. Up to 3% of patients also developed a urethrorectal fistula.

17.9.4 Salvage Cryosurgical Ablation

Salvage cryosurgery might be an alternative to local salvage using surgery or HIFU. The device improvement with the argon/helium-gas-based cryotherapy is the standard technology. Most available data are single-center based, with less than 1,000 reported patients (Kimura et al. 2009). The median follow-up ranges from 12 to 39 months, leading to 5-year disease-free survival between 44% and 73%. As with salvage brachytherapy, the failure definition was not uniform, limiting the interpretation. Pretreatment D'Amico risk classification is an important predictive factor of efficacy (Ismail et al. 2007), as are the pretreatment PSA (<10 ng/ml) and biopsy Gleason score (<7) (Chin et al. 2001; Pisters et al. 2008). This modality is associated with significant side effects, especially urinary incontinence (ranging from 4% to 40%, with 2–4% severe incontinence), obstruction, or retention (from 0% to 21%). With the use of thermocouples and the third-generation device, the recto-urethral fistula incidence is around 1–2% and still decreasing.

17.9.5 Local Salvage: How to Choose?

The most effective local salvage modality appears to be salvage radical prostatectomy. However, its use is limited with its technical difficulties and high complication rate. Less-invasive procedures are appealing. It must be recognized that even if less toxic, they are not associated with long-term results and large multicenter cohorts. The most studied minimally invasive procedure so far appears to be the third-generation cryotherapy; also, this does not mean that it is the most effective. Large prospective trials with universally accepted failure definition are urgently awaited.

Finally, if local salvage is considered, these minimally invasive modalities could be used as focal salvage, provided an effective imaging of the intraprostatic recurrence (Rouviere et al. 2010).

17.9.6 Salvage ADT After Radiotherapy

Clear data regarding the effectiveness of salvage ADT after radiotherapy are lacking. One of the largest cohorts is retrospective, based on 248 patients (ASTRO definition) (Pinover et al. 2003). The use of salvage ADT was associated with a clear benefit in terms of metastasis-free survival at 5 years (57% compared to 78%, $p = 0.0026$),

but only for those having a PSA-DT < 12 months. No survival benefit was seen in any group.

Long-term ADT is associated with significant side effects. Using an intermittent modality might be beneficial. The recently presented SWOG-JPR7 trial answers this specific question (Klotz et al. 2011). This large cohort of 1,340 patients relapsing after radiotherapy (either primary of following radical prostatectomy), was able to show a noninferiority of IAD compared to continuous ADT (median overall survival of 9.1 years in the continuous compared to 8.8 years in the intermittent arm) ($p = 0.009$ for noninferiority). After an 8-month induction period using an LHRH analogue combined with a nonsteroidal antiandrogen for 1 month, patients were randomized between IAD and continuous ADT in the absence of clinical progression, and the PSA was below 4 ng/ml. In the IAD arm, the ADT was stopped and resumed when the PSA went above 10 ng/ml for fixed 8-month periods. Other benefits apart from less drug were observed, such as an improved quality of life in the intermittent arm. The full paper is awaited.

17.10 Salvage After First-Line HIFU

Although, first-line HIFU is still a matter of intense debate, and salvage radiotherapy after failed HIFU seems to be effective. The largest cohort (Riviere et al. 2010) of 100 patients (83 patients without any form of ADT) after a median 33 months of follow-up showed an overall 72.5% relapse-free survival at 5 years without ADT. The D'Amico classification was predictive of relapse-free survival, as were the PSA nadir and time to nadir postsalvage. The toxicity was acceptable (7.1% GU grade 3 or above).

17.11 Conclusion

Any form of salvage treatment must be balanced by the natural history of the individual relapse, the expected benefit (PSA relapse-free survival, metastasis-free survival, or cancer-specific survival), and the individual overall life expectancy. Apart from treating patients and sometimes doctor's anxiety, treating the PSA only is no longer acceptable. A clear and real benefit must be expected and accepted by the patient before embarking into any form of treatment.

Following surgery, even if effective at relapse, the optimal timing of postoperative radiotherapy remains unclear. If considered at salvage, it should be used as early as possible. Based on the recognized importance of local control to decrease the metastasis rate and increase the overall survival, it must be systematically considered in patients with a low PSA-DT, as long as survival is the main objective. For slow-growing PSA, its survival impact is as best questionable. The clinical benefit of salvage ADT remains questionable except in the most aggressive situations (Gleason > 7 and/or PSA-DT < 12 months), as long as metastasis-free survival is the main objective. No survival benefit has ever been observed. And the PSA response must be balanced against the long-term side effects of ADT. IAD should be considered as the new standard. In 2011, the combination of ADT and external beam at salvage remains experimental.

Following radiotherapy, salvage prostatectomy is a surgically challenging but effective secondary treatment with curative intent. It must be restricted to those young patients with the highest probability of long-term cure, i.e., as soon as possible after relapse, with a PSA < 4 ng/ml, a PSA-DT > 12 months, and a postradiotherapy Gleason score < 8. Other local salvage modalities (brachytherapy, cryotherapy, or HIFU) must still be considered as experimental. Systemic salvage after radiotherapy is based on ADT, even if convincing data are lacking. As for surgery, only those with a PSA-DT < 12 months might benefit from early use. No survival benefit has ever been observed. IAD should be considered as the new standard.

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