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Tumour Review

Managing postoperative biochemical relapse in prostate cancer, from the perspective of the Francophone group of Urological radiotherapy (GFRU)

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ABSTRACT

Up to 50% of patients treated with radical surgery for localized prostate cancer may experience biochemical recurrence that requires appropriate management. Definitions of biochemical relapse may vary, but, in all cases, consist of an increase in a PSA without clinical or radiological signs of disease. Molecular imaging through to positron emission tomography has taken a preponderant place in relapse diagnosis, progressively replacing bone scan and CT-scan. Prostate bed radiotherapy is currently a key treatment, the action of which should be potentiated by androgen deprivation therapy. Nowadays perspectives consist in determining the best combination therapies, particularly thanks to next-generation hormone therapies, but not exclusively. Several trials are ongoing and should address these issues. We present here a literature review aiming to discuss the current management of biochemical relapse in prostate cancer after radical surgery, in lights of recent findings, as well as future perspectives.

Introduction

Radical prostatectomy (RP) is among the curative treatments of choice for localized prostate cancer (PCa), including intermediate-risk and well-selected high-risk cases. Nevertheless, up to 50% of patients may experience a prostate specific antigen (PSA) increase after surgery, with no clinical or radiological signs [1]. This situation, known as biochemical recurrence (BCR), should benefit from appropriate management. This review article aims to summarize the management of biochemical recurrence after RP, discussing strategy at diagnosis, current therapeutic options, and future prospects, from the perspective of the Francophone Group of Urological Radiotherapy (GFRU).

There are several definitions of BCR after RP

BCR consists in an elevation of PSA that was previously undetectable after RP, with no clinical or radiological evidence of recurrence. Several definitions of BCR after RP exist, and a literature review could list dozens different ones [2]. One of the most commonly used and adopted by the American Urological Association (AUA) guidelines is a PSA level

Abbreviations: BCR, biochemical recurrence; PBRT, prostate bed radiotherapy; RP, radical prostatectomy, HT, hormone therapy.

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≥ 0.2 ng/mL, confirmed by a second consecutive assay [3]. The European Association of Urology (EAU) guidelines adopted a PSA level ≥ 0.4 ng/mL instead [4], which seemed to have a better correlation with metastatic progression [5]. However, some authors have proposed lower thresholds for PSA levels (starting from 0.05 ng/mL) in order to obtain the best possible sensitivity, but without robust evidence of clinical relevance [6].

At the time of recurrence, it is necessary to take into account several prognostic factors, namely prior to recurrence and at recurrence PSA levels, time to BCR, PSA doubling time, ISUP grade derived from histopathologic grade, pT category, positive surgical margins, extracapsular extension, seminal vesicle invasion, and lymph node involvement [7]. For instance, distant metastatic recurrence is associated with high ISUP grade, pT category, and PSA levels at recurrence, with positive surgical margins, and with a short PSA doubling time, whereas cancer-specific and all-cause mortality were more specifically associated with a short interval between curative treatment and recurrence, with a short PSA doubling time, and with a high ISUP grade [8]. Among those different prognosis factors, the PSA doubling time and the ISUP grades were identified as the two preponderant ones associated with mortality. The EAU guidelines currently suggests separating patients at low risk (PSA doubling time > 1 year and ISUP grades 1–3) and those at high risk (PSA doubling time ≤ 1 year or ISUP grades 4–5) [4]. In this way, the 5-year rates of MFS and CSS were 97.5% and 99.7% for patients at low risk, and 86.7% and 93.8% for patients at high risk, respectively [9].

The purpose of a radical treatment in oncology is to extend the time without disease, and ultimately the patient's life expectancy. This is why studies about cancers aim to demonstrate a reduction in mortality after a curative intervention. Such demonstration can require very long follow-up in PCa, and surrogate endpoints, often validated through the Prentice criteria [10], could provide earlier results. For example, data from the RTOG 9202 trial could firstly determine that the distant metastasis and clinical treatment failure at 3 years could be surrogate endpoints for cancer-specific survival (CSS) at 10 years [11], and secondly that the time interval free of BCR could be a surrogate endpoint for CSS and overall survival (OS) [12]. Data from the RTOG 9601 trial confirmed that BCR (using different definitions), occurrence of distant metastasis, and metastasis-free survival (MFS) satisfied the Prentice criteria, and emphasized the correlation between MFS and OS was the strongest, whereas the correlation between BCR and OS was weak [13]. Xie et al. performed a *meta*-analysis, which also showed that MFS was a strong surrogate for OS [14], whereas event-free survival (EFS) that is a composite endpoint including biochemical and clinical recurrence and death was not [15]. Gharzai et al. found consistent results in their *meta*-analysis and confirmed that only MFS was a validated surrogate endpoint for OS in PCa [16]. As a matter of fact, only 12% of patients presenting a BCR will develop metastasis and 6% will die from their PCa [17]. Besides, other endpoints, notably treatment-related ones, should be considered with for instance time to re-treatment or time without treatment (notably androgen deprivation), since interventions can alter patients' quality of life [18], and consequently impact survivorship [19,20]. In summary, BCR is therefore not the most reliable surrogate endpoint to reflect patient morbidity and mortality but has the advantage to be easily and quickly assessable.

Molecular imaging has an increasing role in BCR PCa

The diagnosis of BCR should exclude metastatic recurrence, which corresponds to distant dissemination of the disease with secondary lesions that can be detected on conventional imaging (CT and bone scans). Because of its increased sensitivity compared to conventional imaging, molecular imaging with positron emission tomography (PET) has become increasingly important for detecting PCa metastasis [21]. PET can effectively detect more distant recurrences that would have gone undetected and can then cause treatment plan to change timely or not, knowing that patients without findings in PET respond very well to prostate bed radiation therapy, unlike those with positive findings in PET [22]. There are several tracers that can be used in PCa such as choline, fluciclovine and prostate specific membrane antigen (PSMA).

^{18}F-choline and ^{11}C-choline are two available radiopharmaceuticals with no significantly different performances, as shown in a *meta*-analysis [23]. The sensitivity of choline-PET exceeds 80% in several studies, but its performance is very dependent on the PSA level at relapse with a low detection rate in case of PSA levels of<1 ng/mL [24], and also dependent on both PSA doubling time and PSA velocity [25,26].

^{18}F-fluciclovine has also demonstrated good performances, capable of changing patient management, including the choice of radiotherapy volumes [27,28,29]. The EMPIRE-1 phase II/III trial even showed an improvement in 3-year recurrence-free survival in patients who underwent fluciclovine-PET compared to those who underwent conventional imaging (75.5% versus (vs) 63%, p = 0.0028) [30].

PSMA-ligands are radiopharmaceuticals that have the advantage of maintaining a good detection rate even in cases of low PSA levels (up to 45% detection rate with a PSA ≤ 0.5 ng/mL) [31], and high inter-reader agreement for recurrent PCa [32]. Prospective studies highlighted the superiority of PSMA over choline [33] and fluciclovine [34]. A *meta*-analysis comparing choline, fluciclovine, and PSMA found detection rates of 34%, 37%, 44% for PSA of <0.50 ng/mL, 36%, 44%, 60% for PSA between 0.50 and 0.99 ng/mL, and 50%, 61%, 80% for PSA between 1.0 and 1.99 ng/mL, respectively [35]. The development of PSMA-PET was initially hampered by the fact that PSMA had to be coupled to gallium-68 (^{68}Ga-PSMA-11), and few centers had the necessary human and material resources. This obstacle is starting to be circumvented by the use of PSMA coupled with fluor-18 (^{18}F-DCFPyL), which has comparable performances and is more readily available in nuclear medicine centers [36,37]. These radionuclides could thus be selected indiscriminately, given the lack of evidence supporting any superiority [38]. Other radiopharmaceuticals based on PSMA will be available, such as ^{18}F-PSMA-1007 that has preferential biliary elimination, or ^{18}F-rhPSMA-7 that has low bladder retention, enabling a correct uptake detection in the pelvis due to the low impact of a weak bladder activity [39,40]. A review highlighted the performances of ^{18}F-PSMA-1007 PET to detect local recurrence and pelvic nodes, but warned about unspecific skeletal fixations mimicking metastasis [41]. Besides, Emmett et al. showed that negative findings in ^{68}Ga-PSMA-11 PET were an independent factor predicting for a high response to salvage prostate bed RT and that the results could prognosticate outcomes like freedom progression [42,43]. From the above results, we can conclude that the exam of choice for staging, in patients with BCR, is currently PSMA-PET, notably in patients with low PSA levels (<1 ng/mL) as recommended by the EAU guidelines [44], despite the lack of proven oncologic benefit associated with treatment modifications based on imaging results.

Radiation therapy (RT) is a central treatment for BCR

Recurrent PCa used to be treated by hormone therapy (HT) alone [45]. The TOAD trial suggested introducing HT as soon as a rising PSA was detected, since immediate intervention showed an improvement in OS compared to delayed intervention (HR = 0.55, 95%CI [0.30–1.00], p = 0.05) [46]. However, such treatment (whether it is continuous or intermittent) is associated to short- and long-term adverse effects, notably skeletal and cardiovascular ones, and alters the patients' quality of life [47,48]. Prostate bed RT then appeared to be a more relevant alternative. In fact, RT showed its benefits in several retrospective studies, which found a decrease in local recurrence (HR = 0.13, 95%CI [0.06–0.28], p < 0.0001) and metastatic progression (HR = 0.24, 95%CI [0.13–0.45], p < 0.0001) [49], as well an improvement in CSS (HR = 0.32, 95%CI [0.19–0.54], p < 0.001) [50], when compared to observation. A retrospective analysis even showed improved OS in patients receiving salvage RT, a benefit that was consistent after adjustment for PSA doubling time and cardiac comorbidities [51]. Moreover, the

JCOG0401 study was a phase III randomized trial that compared RT to a systemic treatment with bicalutamide. It managed to show an improvement in biochemical recurrence-free survival (bRFS) thanks to RT (median = 8.6 years) compared to bicalutamide (median = 5.6 years) (HR = 0.56, 95%CI [0.40–0.77], $p < 0.001$), but no significant benefit in clinical recurrence-free survival (cRFS) (HR = 0.90, 95%CI [0.45–1.81], $p = 0.77$), or OS (HR = 1.03, 95%CI [0.46–2.30], $p = 0.94$) [52]. Despite the lack of benefit in OS from prospective studies, prostate bed RT has established itself as a reference treatment for BCR.

Target volumes of RT require accurate definitions

Volumes of RT to discuss are post-surgical prostate bed and pelvic lymph nodes, and different delineation guidelines have been suggested. In order to limit delineation variability, the Francophone Group of Urological Radiotherapy (GFRU) did a synthesis of the recommendations from four guidelines to delineate the prostate bed [53,54,55,56,57], while the NRG oncology group and the GFRU suggested an updated atlas for pelvic nodes, given the need of revising their volumes [58,59,60]. Delineating according to the GFRU and NRG oncology group recommendations was externally validated, since target coverage was more accurate compared to the previous RTOG guidelines [61,62].

Pelvic elective node irradiation (ENI) is a debated topic. Retrospective studies showed benefits in bRFS thanks to additional ENI compared to prostate bed alone, knowing that these studies were limited to patients with either high-risk disease [63,64] or a PSA level ≥ 0.4 ng/mL [65]. These findings were further supported by a multi-institutional retrospective study analyzing over 1800 patients who underwent salvage RT [66]. With a median follow-up of 51 months after treatment, ENI was associated to a 13% absolute improvement in bRFS, and to 16% in the subset of patients with a Gleason score of 8–10 disease. Moreover,

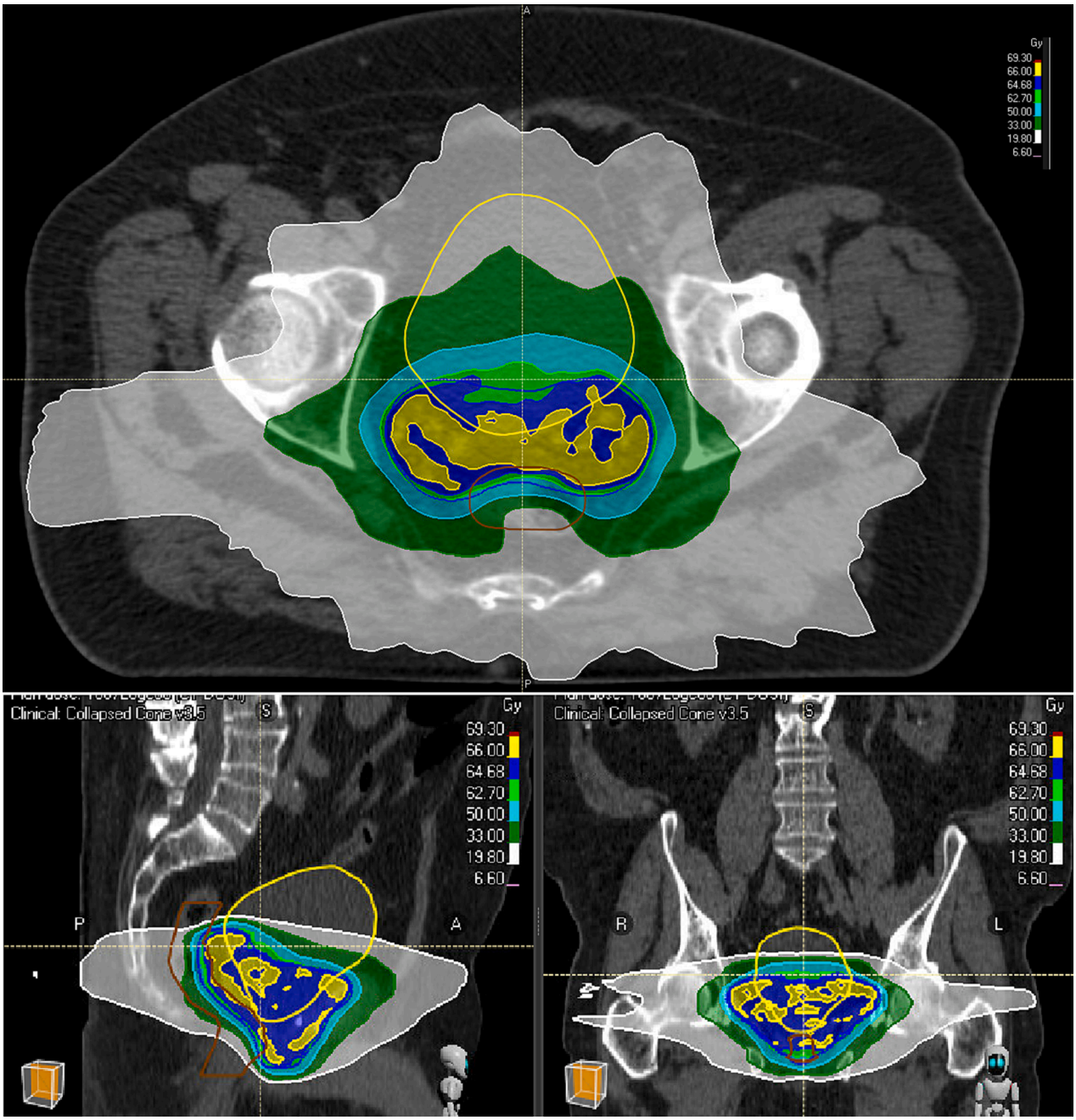

Fig. 1. Illustration of a radiotherapy plan from a patient treated by 66 Gy (in 33 daily fractions of 2 Gy) in prostate bed.

the RTOG 0534 SPPORT trial investigated the benefits of pelvic ENI by randomizing 1792 patients into three arms: prostate bed RT (arm 1), prostate bed RT + HT (arm 2), prostate bed and pelvic nodes RT + HT (arm 3) [67]. In this study the results should be carefully interpreted and considered as significant based on a one-sided $p < 0.0125$, given the alpha risk inflation in a three-arm comparison. PFS, which was the primary endpoint, did not differ significantly between arms 2 and 3 (HR = 0.82, CI [0.63–1.07], p = 0.048), and in sensitivity analysis, no subgroup seemed to benefit significantly from the additional pelvic irradiation either. For the secondary endpoints, head-to-head comparison did not find any difference between these three arms in OS, nor in MFS. The superiority of arm 3 over arm 2 was thus not statistically significant, whereas acute adverse effects were more frequent in arm 3, making it difficult to definitively recommend pelvic irradiation in all patients.

Figs. 1 and 2 below illustrate the radiotherapy plans of patients treated in prostate bed only and in prostate bed plus pelvic nodes, respectively. The treatment was delivered in Volumetric Modulated Arc Therapy (VMAT), an intensity-modulated technique enabling adjacent organs at risk (OARs) preservation.

The planned target volume (PTV) of the prostate bed is delineated in dark blue lines, whereas the organs at risk (OARs) are delineated in brown lines for the rectum and yellow lines for the bladder. The isodoses that represent the dose distribution are displayed in colorwash for an easy visualization.

The PTV of the prostate bed is delineated in dark blue lines and the PTV of pelvic nodes in red lines, whereas the OARs are delineated in brown lines for the rectum and yellow lines for the bladder. The isodoses that represent the dose distribution are displayed in colorwash for an easy visualization.

Several RT regimens exist

The question about dose escalation of RT was a subject of interest. A Chinese trial that enrolled 144 patients did not find any difference in 4-year bRFS between the cohorts receiving an intensified dose in the prostate bed of 72 Gy and a standard dose of 66 Gy (82.6% vs 75.9% respectively; p = 0.299), nor in acute and late grade ≥ 2 toxicities [68]. Similarly, the SAKK 09/10 trial randomized 350 patients to test an

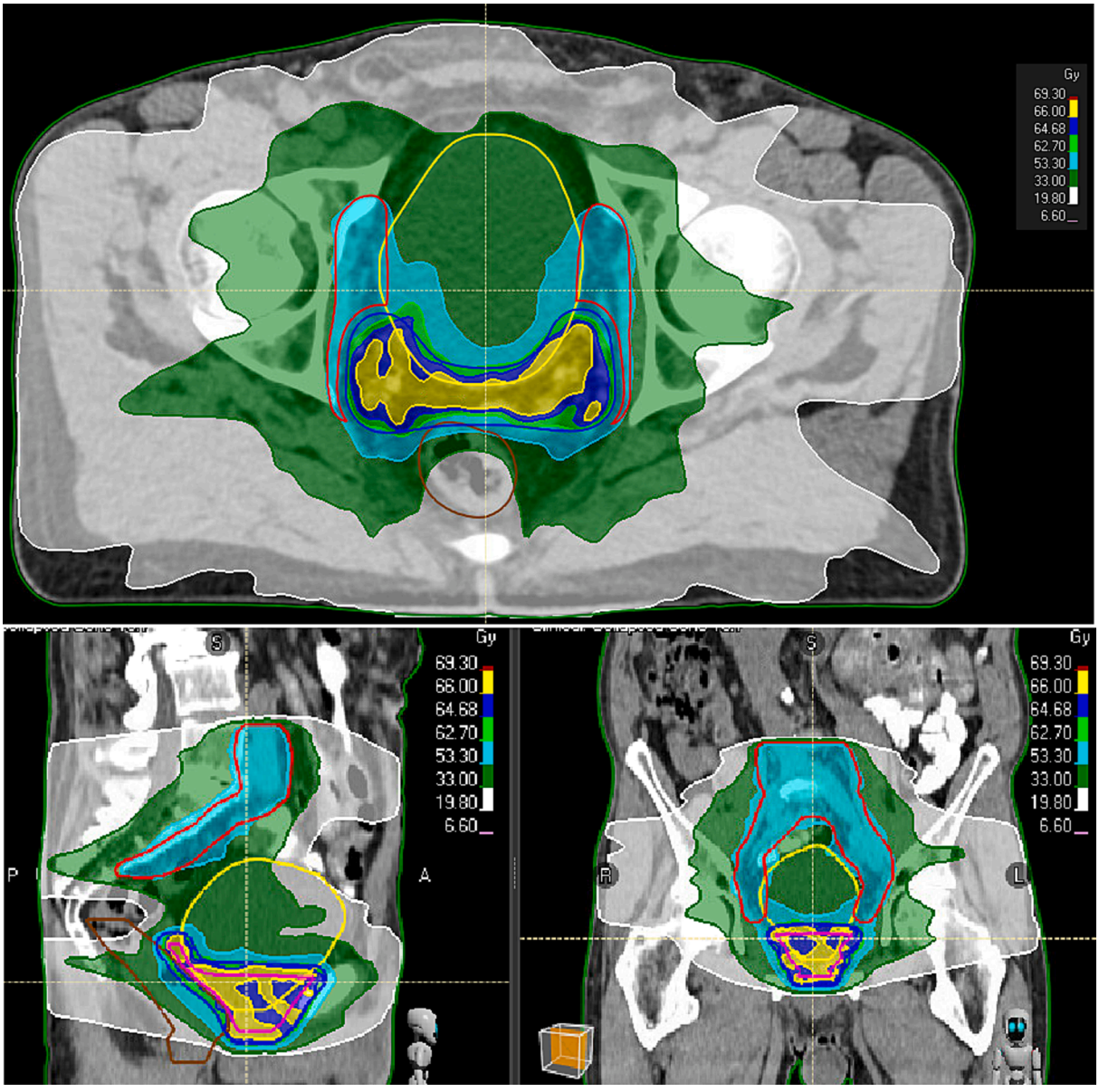

Fig. 2. Illustration of a radiotherapy plan from a patient treated by 56.1 Gy (in 33 daily fractions of 1.7 Gy) in pelvic nodal areas and simultaneously by 66 Gy (in 33 daily fractions of 2 Gy) in prostate bed.

intensified dose of 70 Gy compared to a standard dose of 64 Gy (with 2 Gy per session). The medians for bRFS did not significantly differ and were 7.6 years in the 70 Gy arm and 8.2 years in the 64 Gy arm (HR = 1.14, 95%CI [0.82–1.60], p = 0.4). There was also no difference in MFS and OS, but there was an excess of grade ≥ 2 gastrointestinal toxicity in the 70 Gy arm, reflecting a lack of interest in escalating the dose delivered to the whole prostate bed [69]. However, a focal dose escalation in a macroscopic local relapse may be an option, since the SPIDER retrospective study showed an improvement in 5-year PFS in this case [70].

Besides, hypofractionated RT may deserve attention. Beyond economic and pragmatic considerations due to a reduced number of treatment sessions, hypofractionation relies on a strong biological rationale. While the value of the α/β ratio in PCa is debated, there is agreement that this ratio is low, reflecting a greater sensitivity to dose per fraction [71]. A *meta*-analysis reported studies evaluating moderate hypofractionation, with doses per fraction ranging from 2.3 Gy to 3.5 Gy, and suggested its feasibility but with a low level of evidence due to limited numbers of patients [72]. A retrospective study of 112 patients found comparable disease control between the standard normofractionated regimen and a hypofractionated regimen delivering 52.5 Gy in 20 fractions (approximately 2.6 Gy per fraction), and this with 10-year follow-up [73]. From a monocentric cohort of 1176 men, Cozzarini et al. highlighted higher rates of late grade ≥ 3 urinary toxicities (18% at 5 years) related to the use of moderately hypofractionated regimens [74], which is the main drawback expected when reducing the number of fractions. A comparative study of 461 men also found that patients with a hypofractionated regimen (receiving 2.5 Gy per fraction) presented late grade ≥ 3 urinary toxicities more often than with conventional fractionation (11% at 6 years vs 4%, p = 0.0081) [75]. However, another monocentric cohort of 854 patients receiving 70 Gy in 28 fractions (2.5 Gy per fraction) found low rates of severe toxicities (grade ≥ 3 urinary and digestive toxicities of 2% and 1% at 10 years, respectively) [76]. Patients in the RADICALS-RT trial could receive a hypofractionated regimen (52.5 Gy in 20 fractions), representing 34% of the included patients and an exploratory analysis reported the toxicity. Grade 3–4 toxicities were scarce and comparable between the hypofractionated and conventional regimens. The only difference was grade 1–2 cystitis during the first two years (20% with hypofractionated regimen vs 30% with conventional regimen; p = 0.04), but the significance faded after these two years [77]. The NRG Oncology GU003 trial was a phase III trial randomizing 296 patients between normofractionated (66.6 Gy in 37 fractions) and hypofractionated (62.5 Gy in 25 fractions) regimens [78]. The two groups were comparable in terms of genitourinary and gastrointestinal toxicities. The hypofractionated regimen was not inferior in terms of RFS, although the median follow-up of 2 years was too short to conclude definitively and long-term results should be expected. There is even less data in the literature for more severe hypofractionation, which can propose shortened regimens of up to 5 fractions, and doses per fraction of up to 9 Gy. For instance, the SCIMITAR single-arm trial reported low toxicity at short-term in one hundred patients receiving 30 to 34 Gy in 5 fractions in prostate bed [79]. Table 1 below shows other hypofractionation regimens being evaluated. Given the encouraging preliminary results of these studies with few patients included, higher powered trials should follow [80].

Table 1
Hypofractionated regimens for prostate bed radiotherapy *Abbreviations: fr (fractions), Gy (Grays), MTD (maximum tolerated dose), QoL (quality of life), GU (genitourinary), GI (gastrointestinal), bRFS (biochemical recurrence-free survival, MFS (metastasis-free survival), OS (overall survival).*

Study	Phase	Patients	Regimens	Endpoint	Results
Wages et al. [81]	I/II	32	20 fr × 2.83 Gy 15 fr × 3.36 Gy10 fr × 4.26 Gy	MTDQoL	MTD = 10 fr × 4.26 GyQoL decreased
Leite et al. [82]	II	61	15 fr × 3.4 Gy	GU and GI toxicitiesbRFS, MFS, OS	Acceptable toxicities
Ballas et al. [83]	I	24	15 fr × 3.6 Gy 10 fr × 4.7 Gy5 fr × 7.1 Gy	MTD	MTD = 5 fr × 7.1 Gy
Sampath et al. [84]	I	26	5 fr × 7 Gy 5 fr × 8 Gy5 fr × 9 Gy	MTD	MTD = 5 fr × 8 Gy

Timing of RT should be optimized

The question about the adequate timing of RT was addressed by trials comparing adjuvant RT (within 6 months after RP) and early salvage RT (when PSA rises), the results of which are presented in Table 2 below.

The RADICALS-RT trial found no difference in BCR between the two groups, but reported a significant excess of genitourinary toxicity (notably incontinence and grade 3–4 urethral stricture) in the adjuvant RT arm [85]. The RAVES trial found that salvage RT was non-inferior in terms of biochemical control and was associated to lower genitourinary toxicity [86]. The GETUG-AFU 17 trial found no benefit in terms of EFS and reported an excess of genitourinary toxicity and late erectile dysfunction in the adjuvant arm [87]. By pooling the results of these three trials, the ARTISTIC *meta*-analysis group considered early salvage RT as the standard treatment, since delaying RT could avoid potentially severe adverse effects without compromising disease control [88]. Nevertheless, these results are mainly based on biochemical instead of clinical outcomes, and a low proportion of patients with high-risk features (with pT3-4, pN1, or ISUP grades 4–5). As a matter of fact, by emulating a hypothetical trial, Schaufler et al. suggested that adjuvant RT led to a theoretical improvement in OS for patients with ISUP grades 4–5, two or more pathological nodes, or negative surgical margins [89]. Besides, a cohort composed of thousands of men treated for PCa in Germany retrospectively showed that patients with these high-risk features had better OS when treated by adjuvant RT in comparison to salvage RT [90]. Adjuvant RT also seemed to decrease all-cause mortality in pN1 patients, with higher benefits correlated to a higher number of positive pathologic lymph nodes [91]. Adjuvant RT may therefore have an indication in selected cases of patients presenting high-risk features.

The benefits of combining RT with HT

Despite prostate bed RT, about half of patients may still relapse, prompting a will to intensify treatment [92]. Four phase III trials have contributed to demonstrate the benefits of adding HT to post-operative RT, the results of which are presented in Table 3 below.

The RTOG 9601 trial demonstrated improved OS with the addition of 24 months of bicalutamide [93]. Nevertheless, sensitivity analyses did not confirm this benefit in the subgroup of patients with PSA ≤ 0.6 ng/mL, and emphasized an excess of severe cardiac and neurological toxicities associated with long-term HT [94]. Besides, it is classically accepted that salvage RT should be proposed early for optimal disease control, if possible before the PSA exceeds 0.5 ng/mL [95]. It was also suggested that the addition of HT would correct for the delay in diagnosis, giving RT good efficacy even in case of late salvage [96]. The GETUG-AFU 16 trial demonstrated an improvement in PFS and MFS with the addition of 6 months of goserelin, a benefit that was also found in post-hoc analyses after risk stratification [97]. The RTOG 0534 SPPORT trial randomized 1792 patients into three arms: prostate bed RT (arm 1), prostate bed RT + HT (arm 2), prostate bed and pelvic lymph nodes RT + HT (arm 3) [67]. Compared to RT alone, arms 2 and 3, which received 4 to 6 months of HT, had significantly better PFS. In subgroup

Table 2
Randomized phase III trials comparing adjuvant versus early salvage radiotherapy Patients in arms with adjuvant RT received RT within 6 months after prostatectomy. *Abbreviations: RT (radiotherapy), fr (fractions) HT (hormone therapy), bRFS (biochemical recurrence-free survival), EFS (event-free survival).*

Study	Patients	Treatment arms	RT dose	Pelvic nodal irradiation	HT use	Results	p-value	Hazard Ratio	Patients in the salvage arm that did not require RT
RADICALS-RT	1396	*Arm 1:* Adjuvant RT *Arm 2:* Salvage RT(when PSA ≥ 0.1 ng/mL or 3 consecutives rises)	66 Gy in 33 fr or52.5 Gy in 20 fr	Arm 1: 7% Arm 2: 3%	At discretion	*5-year bRFS* *Arm 1:* 85% *Arm 2:* 88%	0.56	1.10; 95%CI [0.81–1.49]	67% within a medianfollow-up of 4.9 years
TROG 08.03/ ANZUP RAVES	333	*Arm 1:* Adjuvant RT *Arm 2:* Salvage RT(when PSA ≥ 0.2 ng/mL)	64 Gy in 32 fr	No	No	*5-year bRFS* *Arm 1:* 86% *Arm 2:* 87%	0.15	1.12; 95%CI [0.65–1.90]	50% within a medianfollow-up of 6.1 years
GETUG-AFU 17	424	*Arm 1:* Adjuvant RT *Arm 2:* Salvage RT(when PSA ≥ 0.2 ng/mL)	66 Gy in 33 fr	Arm 2: 24%	Yes (6 months of triptorelin)	*5-year EFS* *Arm 1:* 92% *Arm 2:* 90%	0.42	0.81; 95%CI [0.48–1.36]	46% within a medianfollow-up of 6.5 years

Table 3
Randomized phase III trials evaluating hormone therapy in combination with radiotherapy * Note that the results of RADICALS-HD presented here are from an interim analysis at 5 years. *Abbreviations: PB (prostate bed), RT (radiotherapy), HT (hormone therapy), OS (overall survival), PFS (progression-free survival), MFS (metastasis-free survival).*

Study	Patients	Treatment arms	Primary outcome	Results	p-value	Hazard Ratio
RTOG 9601	760	*Arm 1:* PB RT alone *Arm 2:* PB RT + 24 months HT	12-year OS	*Arm 1:* 71.3% *Arm 2:* 76.3%	0.04	0.77; 95%CI [0.59–0.99]
GETUG-AFU 16	743	*Arm 1:* PB RT alone *Arm 2:* PB RT + 6 months HT	10-year PFS	*Arm 1:* 49% *Arm 2*: 64%	<0.0001	0.54; 95%CI [0.43–0.68]
RTOG 0534SPPORT	1792	*Arm 1:* PB RT alone *Arm 2:* PB RT + 4–6 months HT *Arm 3:* PB and pelvic RT + 4–6 months HT	5-year PFS	*Arm 1:* 70.9% *Arm 2:* 81.3% *Arm 3:* 87.4%	*Arms 2* vs *1:* <0.0001 *Arms 3* vs *1:* <0.0001 *Arms 3* vs *2:* 0.048	0.60; 97.5%CI [0.47–0.77] 0.50; 97.5%CI [0.39–0.64]0.82; 97.5%CI [0.63–1.07]
RADICALS HD*	2839	*Arm A1:* PB RT alone *Arm A2:* PB RT + 6 months HT *Arm B1:* PB RT + 6 months HT *Arm B2*: PB RT + 24 months HT	10-year MFS	*Arm A1:* 79% *Arm A2:* 80% *Arm B1:* 72% *Arm B2:* 78%	*Arms A2* vs *A1:* *Arms B2* vs *B1:*	0.89; 95%CI [0.69–1.14]0.77; 95%CI [0.61–0.97]

analysis stratified by baseline PSA, ISUP grades, pT, and seminal vesicle involvement, PFS was significantly better in arm 2 than in arm 1 in all subgroups but ISUP grades 4–5 patients, and was significantly better in arm 3 than in arm 1 in all subgroups. Compared to RT alone, arms 2 and 3 also decreased both local and regional failure. The arms with HT thus had significantly better outcomes. The RADICALS-HD trial aimed to determine the optimal duration of HT by comparing three arms of treatment: RT alone, RT + short-term (6 months) HT, and RT + long-term (24 months) HT (ClinicalTrials.gov: NCT00541047). The primary outcome was MFS and the results after a median follow-up of 9 years were firstly presented during the ESMO (European Society for Medical Oncology) Congress 2022 [98]. Comparing none vs short-term HT, there was no difference in MFS (HR = 0.89, 95%CI [0.69–1.14]) or in OS (HR = 0.88, 95%CI [0.65–1.19]). Comparing short-term vs long-term HT, long-term HT significantly improved MFS (HR = 0.77, 95%CI [0.61–0.97]), but not OS (HR = 0.88, 95%CI [0.66–1.17]). Clinical events are rare in the setting of BCR, which is why the DADSPORT *meta*-analysis pooled the data of these 4 trials, the first results of which were also presented during the ESMO Congress 2022 [99], showing a modest improvement in MFS (only 2 points of difference at 5 years) with short-term HT vs none (HR = 0.82, p = 0.013, 95%CI [0.70–0.96]) whereas data with long-term HT were not available. However, there was no significant improvement in OS with either short-term or long-term HT vs none.

New molecules are under evaluation to potentiate RT

New molecules of HT have been developed to manage PCa. Abiraterone acetate (AA) is a drug that inhibits CYP17, a key enzyme that is involved in androgen synthesis in the gonads, adrenal glands, and prostate [100]. AA combined with first-generation HT was first approved in metastatic castration-resistant cancer [101,102], and then in hormone-sensitive metastatic cancer [103,104], potentially in combination with docetaxel [105]. Enzalutamide, apalutamide, and darolutamide are new direct peripheral androgen receptor antagonists with much greater affinity and cytosolic penetration than older antagonists

such as bicalutamide. These molecules are also approved as treatments for advanced stages [106,107,108,109]. A legitimate question is whether these next-generation HT might have benefits in earlier stage PCa [110]. Table 4 below shows the clinical trials evaluating these new hormonal molecules given concomitantly to salvage RT.

The phase II single-arm STREAM trial tested in 37 patients salvage RT, first-generation HT and enzalutamide and found that 2-year and 3-year PFS were 65% and 53%, respectively [113]. These high rates of relapse could be explained by the PSA threshold defined for relapse (at 0.2 ng/mL) and by a population at high risk with 78% of patients who were pT3-T4, 47% who had ISUP grades 4–5, and 21% who were pN1. CARLHA is a single-arm phase I/II trial, testing in 46 patients salvage RT, goserelin and AA [111]. The oncological outcomes at three years will be available soon. Randomized studies are also published. Autio et al. evaluated the benefits of AA in a phase II trial by randomizing 122 patients with BCR into 3 groups to receive AA or degarelix or both [112]. Compared to degarelix, AA plus degarelix significantly improved the rates of undetectable PSA at 8 months (87.8% vs 66.7%, p = 0.04), but not AA alone (83.8% vs 66.7%, p = 0.12). Compared to degarelix, post-hoc analysis showed an extended time to PSA progression with AA plus degarelix (median of 64.4 vs 54.9 weeks). SALV-ENZA is another phase II trial randomizing 86 patients to receive RT and enzalutamide or placebo for 6 months. The bRFS was significantly improved in the experimental arm (HR = 0.42, 95%CI [0.19–0.92], p = 0.031) with a 2-year rate of 84% vs 66%, and the benefits were more significant in patients with pT3 and with R1 disease compared to patients with pT2 and with R0 disease, respectively [114]. In the FORMULA 509 trial, 345 patients with a high-risk feature (Gleason 8–10, PSA > 0.5, pT3/T4, pN1 or radiographic N1, PSA doubling time < 10 months, negative margins, persistent PSA, gross local/regional disease, or Decipher High Risk) were randomized to receive salvage RT and a 6-month LHRH agonist with either bicalutamide or AA plus apalutamide [115]. A planned primary analysis with a median follow-up of 34 months did not show any significant difference in PFS (HR = 0.71, 90%CI [0.49–1.03], p = 0.06), nor in MFS (HR = 0.57, 90%CI [0.33–1.01], p = 0.05), but results are not definitive yet. However, the subgroup of patients with PSA levels > 0.5 ng/mL had significant improvements in both PFS (HR = 0.50, 90%CI [0.30–0.86], p = 0.03) and MFS (HR = 0.32, 90%CI [0.15–0.72], p = 0.01), thanks to the experimental regimen with AA plus apalutamide. The EMBARK study was a phase III trial assessing the benefits of enzalutamide in patients relapsing after an initial definitive therapy by RP, or RT, or both [116]. Compared to placebo plus leuprolide acetate, the two experimental arms showed a significant improvement in MFS (HR = 0.42, 95%CI [0.30–0.61], p < 0.0001 with enzalutamide plus leuprolide acetate; HR = 0.63, 95%CI [0.46–0.87], p = 0.0049 with enzalutamide monotherapy) [117]. Other controlled trials are ongoing, with for instance the phase III trials CARLHA-2 (NCT04181203) and PRIMORDIUM (NCT04557059) that will evaluate the addition of apalutamide to 6 months of first-generation HT in biochemically relapsing patients at high risk. In summary, only biochemical outcomes are currently available, mainly from phase II trials that are not controlled in some cases, and prescribing next-generation HT in this setting seems precipitous. There is a lack of information about the clinical outcomes and the population to target for treatment intensification.

Other non-hormonal therapies are also being tested

Early-phase studies tested the association of salvage RT with molecules that are not based on hormonal manipulation, but corresponding to chemotherapy, targeted therapies or even biguanides [118]. For example the SAKK 08/15 GETUG-AFU 34 PROMET trial randomized 111 men with recurrent PCa after RP between salvage RT alone or with metformine [119]. Unfortunately, the trial was closed prematurely for financial reasons, and was consequently underpowered to demonstrate any difference in outcomes. Besides, non-hormonal systemic treatments are also being tested without RT, such as immune checkpoint inhibitors, targeted therapies inhibiting PARP, or a combination of both. The Table 5 below shows ongoing trials testing non-hormonal systemic therapies alone, for patients presenting a BCR.

Table 4
Clinical trials evaluating next-generation molecules in combination with radiotherapy *NB: EPIC-26 is a score evaluating patients' sexual function. Abbreviations: bRFS (biochemical recurrence-free survival), PFS (progression-free survival), MFS (metastasis-free survival), ppMPFS (Prostate specific Membrane Antigen-Positron Emission Tomography (PSMA-PET) Metastatic Progression-free Survival)*.

ClinicalTrials.gov number (Trial name)	Molecule	Study design	Patients expected	Primary outcome	Start of inclusion	Expected end of study
NCT01780220 (CARLHA) [111]	Abiraterone	Phase I/II, single-arm, open-label	46	3-year bRFS	December 2012	January 2022
NCT01751451 [112]	Abiraterone	Phase II, randomized, triple-arm, open-label	122	18-month PFS	December 2012	November 2021
NCT02057939 (STREAM) [113]	Enzalutamide	Phase II, single-arm, open-label	38	2-years PFS	April 2014	June 2019
NCT02203695 (SALV-ENZA) [114]	Enzalutamide	Phase II, randomized, double-arm, blinded	96	2-year bRFS	March 2015	January 2023
NCT03141671(FORMULA-509)	Abiraterone + Apalutamide	Phase II, randomized, double-arm, open-label	345	bRFS	May 2017	December 2025
NCT03371719(BALANCE)	Apalutamide	Phase II, randomized, double-arm, blinded	311	bRFS	April 2018	October 2028
NCT03311555(STARTAR)	Apalutamide then Docetaxel	Phase II, single arm, open-label	42	3-year PFS	March 2018	February 2023
NCT03809000(STEEL)	Enzalutamide	Phase II, randomized, double-arm, open-label	242	PFS	April 2019	September 2029
NCT03899077(SAVE)	Apalutamide	Phase II, randomized, double-arm, open-label	202	EPIC-26 score at 9 months	April 2019	September 2022
NCT04181203(CARLHA-2)	Apalutamide	Phase III, randomized, double-arm, open-label	490	5-year PFS	January 2020	December 2033
NCT03777982	Apalutamide	Phase III, randomized, double-arm, open-label	400	2-year MFS	April 2020	December 2034
NCT04423211(INDICATE)	Apalutamide	Phase III, randomized, double-arm, open-label	804	PFS	October 2020	December 2027
NCT04557059 (PRIMORDIUM)	Apalutamide	Phase III, randomized, double-arm, open-label	412	ppMPFS	November 2020	January 2030

Table 5
Active recruiting trials evaluating non-hormonal systemic therapies for biochemical relapse *NB: PSA50 corresponds to the percentage of patients that has a PSA decline ≥ 50%.*

ClinicalTrials.gov number	Molecule	Study design	Patients expected	Primary outcome	Start of inclusion	Expected end of study
NCT04019964	Nivolumab	Phase II, single-arm, open-label	15	PSA50	January 2020	January 2025
NCT03047135	Olaparib	Phase II, single-arm, open-label	50	PSA50	March 2017	February 2023
NCT04336943	Durvalumab + Olaparib	Phase II, single-arm, open-label	30	Undetectable PSA	April 2021	April 2025
NCT03637543	Nivolumab	Phase II, non-randomized, double-arm, open-label	34	Stable or decreasing PSA	October 2018	March 2025

There is a need to better define patients' prognosis to guide treatment escalation

Given the new therapeutics to come, the classification into two risk groups by the EAU may seem limited to make precise decisions regarding treatment escalation, using only clinical and histopathological data. The advances in genomics could provide valuable information [120]. In the post-prostatectomy setting, the Decipher genomic classifier (GC) was validated in several studies, both retrospective and prospective, to be an independent prognostic factor for bRFS, BCR, MFS, CSS and OS [121]. From the SAKK 09/10 trial, 5-year bRFS and clinical PFS rates were respectively about 70% and 80% in patients at low-intermediate GC risk, and 45% and 65% in patients at high GC risk [122]. From patients treated in the RTOG 9601 trial, GC score was interestingly associated to the effect of HT for distant metastasis, CSS and OS. In fact, patients at high GC risk seemed to have 3 times more benefits from the introduction of HT than patients at low GC risk, but the trial was underpowered to reach statistical significance [123]. In the context of next-generation HT at BCR, the PAM50 classifier is another genomic test that will try to identify patients benefiting from the addition of apalutamide in the BALANCE trial (NCT03371719; see Table 4 above). Other biomarkers are being developed [124]. Lau et al. found that detecting circulating tumor DNA in patients treated by RP was a pejorative prognosis factor, and detecting more specifically TP53 mutations was associated to a poorer MFS (HR = 2.4; 95%CI [1.2–4.8], p = 0.014) [125]. After showing relevance in metastatic PCa [126], circulating tumor cells are also being evaluated in earlier stages [127], and the CARLHA trial showed indeed their prognostic value and capacity to discriminate low- and high-risk patients in case of BCR, as orally-presented during the ESTRO (European Society of Radiation Oncology) Congress 2023 (NCT0178022, see Table 4 above).

Another paradigm would be to select patients for treatment de-escalation, as recently commented by Roberts et al., where eligible patients (early BCR and low risk according to EAU classification) could undergo surveillance in case of negative findings in PSMA PET [128], and could then be spared treatment-related toxicities, since RT (and HT) can have a negative impact on urinary function, potency, and quality of life [129]. Such strategy will be evaluated in clinical trials, with for example the DIPPER trial, in order to demonstrate its feasibility and clinical benefits [130].

Table 6
Recommendations of the GFRU members for managing patients with BCR. Recommendations are given with their corresponding strength and level of evidence, according to methodology described by Khalifa et al. [131]. Abbreviations: BCR (biochemical recurrence), cDNA (circulating DNA), CTC (circulating tumor cells), RT (radiotherapy), HT (hormone therapy).

Recommendations	Strengh rating	Level of evidence
For determining patients' prognosis at BCR		
In addition to PSA levels, consider other clinical and pathological features (e.g., ISUP grade, PSA doubling-time)	Strong	A
Genomic classifiers (e.g., Decipher PAM50) could be additional prognostic factors	Moderate	B
Other biomarkers (e.g., cDNA, CTC) could be discussed	Weak	C
For performing imaging exams at BCR		
Molecular imaging (PET) outperforms "conventional imaging" (CT and bone scans)	Strong	A
Prefer PSMA-ligands PET rather than choline or fluciclovine PET for patients with low PSA levels (<1 ng/mL)	Strong	A
Consider novel PSMA-ligands (e.g., 18F-PSMA-1007, 18F-rhPSMA-7) in case of suspected *para*-bladder relapse)	Weak	B
PET findings could help decision making in treatment choices	Strong	B
For planning patients' treatment		
Early salvage RT should be offered to patients with confirmed rising PSA	Strong	A
Adjuvant RT could be discussed in very high-risk patients after RP	Moderate	B
Surveillance could be discussed in low-risk patients with slow PSA rising	Weak	C
Deliver salvage RT without escalating doses in prostate bed (64–66 Gy)	Strong	A
Hypofractionated regimens could be discussed with the patients	Weak	B
Prophylactic pelvic nodal irradiation should be discussed based on the risk of pelvic dissemination	Strong	B
Adding first-generation HT (from 6 to 24 months) should be discussed with all patients and be prescribed after a favorable assessment of benefits/risks ratio	Strong	A
Adding next-generation HT (e.g.,abiraterone acetate, enzalutamide, apalutamide, darolutamide) should be offered to eligible patients as a part of a clinical trial	Strong	B

Conclusion

BCR represent frequent but very heterogeneous situations, and its optimal management remains challenging. Despite being routinely used, RT associated to HT with LHRH agonist is still a matter of debate, notably for determining the optimal duration. Besides, this will be challenged by the results of ongoing trials evaluating the combination of RT with new systemic therapies, hormonal or not. It appears challenging to make definitive guidelines for the management of BCR in PCa. For this purpose, the GFRU expert members tried to suggest recommendations based on current evidence using methodology described by Khalifa et al. [131], for clinical use in routine, and summarized in Table 6. Another approach would be to individualize each patient's treatment instead, thanks to the advances in molecular imaging and innovative biomarkers, which are currently blooming topics and fertile grounds for research. As a matter of fact, making a "one-fits-all" treatment algorithm seems delusional, since benefits of different interventions may vary a lot between patients. The graphical abstract helps identify the main concerns when managing a patient with BCR, and mentions the main trials, which address or will address these issues.

CRediT authorship contribution statement

Loic Ah-Thiane: Conceptualization, Writing – original draft. **Paul**

Sargos: Methodology, Writing – review & editing. **Olivier Chapet:** Writing – review & editing. **Marjory Jolicoeur:** Writing – review & editing. **Mario Terlizzi:** Writing – review & editing. **Carl Salembier:** Writing – review & editing. **Jihane Boustani:** Writing – review & editing. **Célia Prevost:** Writing – review & editing. **Sonya Gaudioz:** Writing – review & editing. **Talar Derashodian:** Writing – review & editing. **Samuel Palumbo:** Writing – review & editing. **Olivier De Hertogh:** Writing – review & editing. **Gilles Créhange:** Writing – review & editing. **Thomas Zilli:** Writing – review & editing. **Stéphane Supiot:** Conceptualization, Supervision, Writing – original draft.

Declaration of Competing Interest

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