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SPECIAL ARTICLE

Local and locoregional prostate cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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INCIDENCE AND EPIDEMIOLOGY

Information on the incidence and epidemiology of prostate cancer and population screening is provided in Supplementary Material Section 1, available at https://doi.org/10.1016/j.annonc.2025.12.009.

Recommendations

- Population-based prostate-specific antigen (PSA) screening can be considered based on national risks and benefits but is associated with a risk of overdiagnosis [I, B].

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnosis

Diagnosis of prostate cancer is primarily based on PSA testing, digital rectal examination (DRE) and imaging to select men for prostate biopsy. Moderately elevated PSA concentrations (3-10 ng/ml) have limited specificity for detection, indicating the need for more accurate biomarkers. PSA-density (PSA-D), derived from PSA level divided by prostate volume, can add value in predicting clinically significant disease.[1] Several blood (e.g. Prostate Health Index, 4K score, IsoPSA, Stockholm3, Proclarix) and urine (e.g. PCA3, SelectMDX, Mi Prostate score, ExoDX) tests have been developed, some of which have been incorporated into screening trials or programmes, or used in clinical settings to some extent.[2] These tests may be considered within risk-stratification pathways to reduce unnecessary prostate biopsy and overdiagnosis, but comparative studies are lacking. Magnetic resonance imaging (MRI) has become an important part of the diagnostic pathway for early detection of prostate cancer before

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biopsy, reducing the risk of overdiagnosis of indolent disease and facilitating accurate biopsy.[3] Diagnostic work-up is shown in Figure 1.

The risk of clinically significant prostate cancer is related to age, ethnicity, family history, PSA level and results of DRE and imaging assessments.[4] Predictive models or risk-stratified algorithms incorporating different clinical parameters (age, PSA level, PSA-D, family history, DRE findings, biomarkers, MRI) can facilitate optimal selection, improve prediction of clinically significant disease and reduce diagnosis of indolent tumours. One example is a risk calculator that was developed based on the European Randomized Study of Screening for Prostate Cancer and updated by incorporating prognostic pathology findings (Gleason score and cribriform growth pattern).[5] It is important, however, that risk calculators are calibrated to the relevant population.

Imaging and biopsy

MRI is recommended before prostate biopsy (initial or repeat).[6-8] Targeted biopsies have a higher detection rate for clinically significant prostate cancer and a decreased detection rate for clinically insignificant disease compared with systematic biopsies.[6,7] The most common definition of clinically significant disease is the presence of International Society of Urological Pathology (ISUP) grade group $\geq$2 (or Gleason score $\geq 3+4$).[6,7] In contrast to transrectal biopsy, transperineal biopsy results in fewer adverse events (AEs) relating to infection and sepsis; it can be carried out without antibiotic prophylaxis,[9] thus aligning with the important issue of antibiotic stewardship.[10] When MRI is positive [i.e. Prostate Imaging Reporting and Data System (PI-RADS) $\geq$4], both targeted and systematic biopsies are required if a high reliability for diagnosis of clinically significant disease is a priority.[7] If reducing the detection of clinically insignificant disease is a priority, targeted biopsy without systematic biopsy may be sufficient.[6,11] Perilesional sampling of the MRI lesion improves detection of clinically significant disease. If MRI is equivocal (PI-RADS 3), biopsy should be carried out if there is a high suspicion of prostate cancer (e.g. high PSA, positive DRE, positive family history) or if PSA-D is $>$0.15.[11] In other cases, biopsy may be omitted based on shared decision making with the patient. High-quality imaging and expertise are mandatory for MRI and biopsy procedures. When multiparametric MRI is of good quality and negative (i.e. PI-RADS $\leq$2) and clinical suspicion of prostate cancer is low, then biopsy may be omitted, taking the individual risk strata and preferences of the patient into account. PSA-D can help to risk stratify patients with a negative MRI for further diagnostic work-up following a non-suspicious MRI result. PSA-D $>$0.15-0.2 signals a higher risk of missed significant prostate cancer in patients with normal MRI findings.[12] In patients at high risk of locally advanced or metastatic disease when systematic biopsy will likely be diagnostic, MRI should not delay diagnosis and treatment; systematic biopsy can be sufficient in these cases.

High-resolution ultrasound (US) based on a 29 MHz transducer can be an alternative to MRI for diagnosis. In a randomised controlled trial (RCT) of 678 patients, high-resolution US-guided biopsies were non-inferior to MRI fusion-guided biopsies for diagnosis of clinically significant prostate cancer (ISUP $>$2).[13] The detection rate with high-resolution US biopsy was 46% versus 43% with MRI fusion biopsy [difference 3.52%, 95% confidence interval (CI) $-$3.95% to 10.92%, non-inferiority $P < 0.001$]. The need for high-quality imaging and expertise also applies to high-resolution US imaging.[13]

Pathology

Biopsy cores should be submitted for histopathological analysis separately, and labelled to confirm the location in the prostate and their targeted or systematic nature.[14] Reports following ISUP grading should include core length, cancer core involvement, Gleason pattern and score and presence of cribriform, intraductal or neuroendocrine subtypes.[14]

Molecular biology

Inherited mutations in *BRCA1* and/or *BRCA2* predispose to the development and aggressiveness of prostate cancer;[15] however, germline testing is not routine clinical practice and is generally reserved for patients with *de novo* metastatic prostate cancer or a family history of breast, ovarian, pancreatic and/or high-risk prostate cancer, and for relatives of patients diagnosed with prostate cancer at a young age. The association of other genes (e.g. *ATM*, *CHEK2*, Lynch syndrome-associated genes) with prostate cancer aggressiveness is controversial. PSA testing every 2-4 years may be considered in individuals aged $\geq$40 years who carry germline mutations that could increase prostate cancer risk. More studies are needed to understand the possible role of polygenic risk scores in screening and early detection pathways.

Recommendations

- Men with sufficient life expectancy ($\geq$10 years) seeking PSA testing can be offered shared decision making, including education about the benefits and harms of early detection, with the decision based on their values and preferences [I, B].
- PSA testing cannot be recommended for asymptomatic men with a life expectancy of $<$10 years [I, D].
- Early detection based on PSA testing and MRI can be recommended for men at high risk of death from prostate cancer, as follows [III, B]:
  - age $\geq$50 years and sufficient life expectancy ($\geq$10 years)
  - age $\geq$45 years with a family history of prostate cancer
  - age $\geq$45 years and of Black African ancestry
  - age $\geq$40 years with *BRCA* mutation
- Germline testing can be recommended for men with multiple family members diagnosed with prostate cancer [III, B].

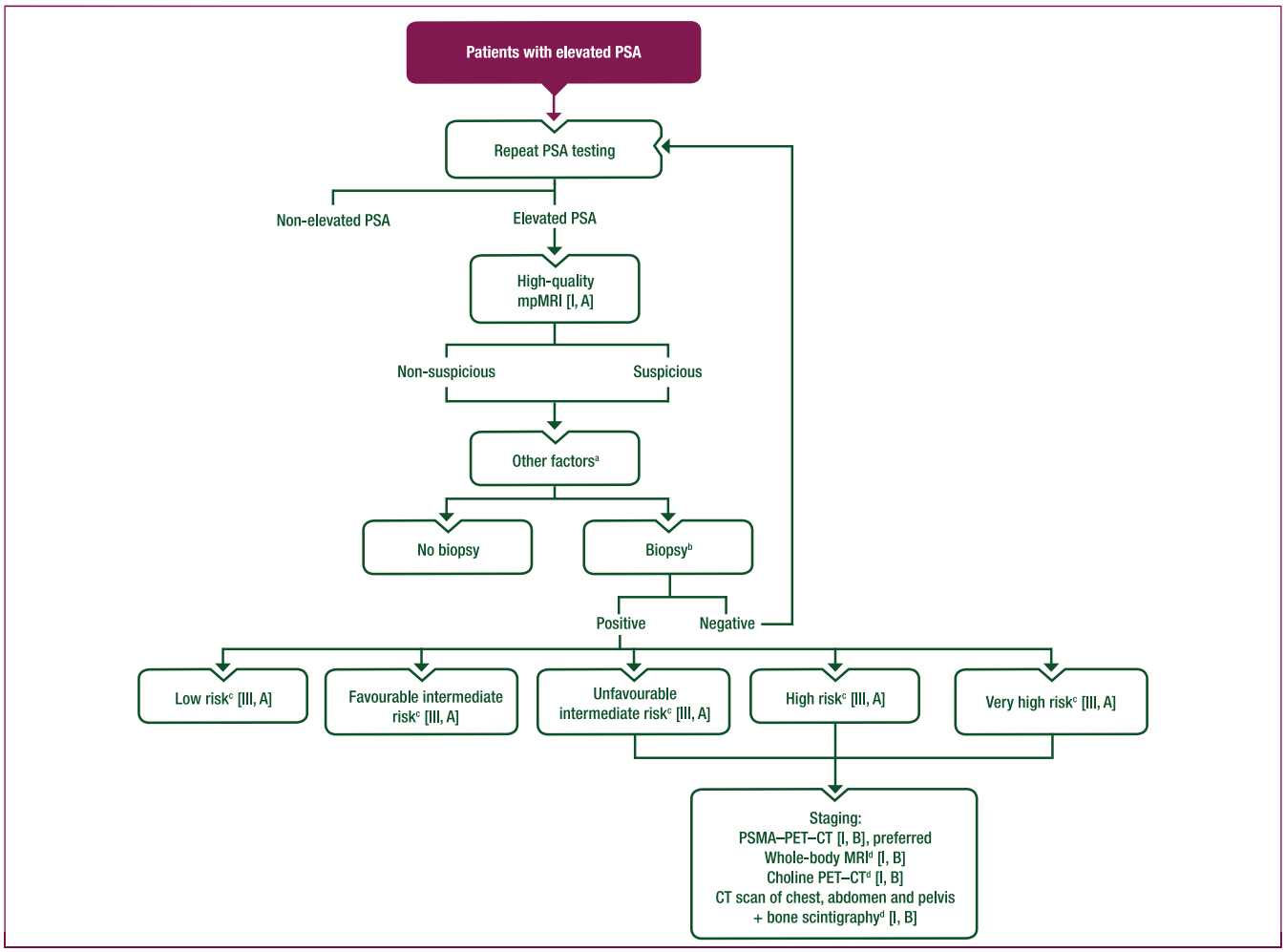

Figure 1. Diagnostic work-up and staging for localised prostate cancer.
Purple: algorithm title; white: other aspects of management and non-treatment aspects.
CT, computed tomography; DRE, digital rectal examination; mpMRI, multi-parametric MRI; MRI, magnetic resonance imaging; PET, positron emission tomography; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.
[a]In addition to PSA level and MRI results, the decision to biopsy or not should be made based on DRE findings, ethnicity, age, comorbidities, free and total PSA, history of previous biopsy and patient values. Biopsy is recommended in patients with a PI-RADS score of 4-5 [I, A], can be recommended in patients with a PI-RADS score of 3 and high-quality MRI [I, B] and is not recommended in patients with a PI-RADS score of $\leq$2, high-quality MRI and low suspicion for prostate cancer [I, E].
[b]Transperineal biopsies are recommended over transrectal ultrasound-guided biopsies [I, A].
[c]See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.12.009, for descriptions of prostate cancer risk groups.
[d]If PSMA–PET is unavailable.

- Risk-stratified pathways, including MRI and PSA-D with or without consideration of a reflex biomarker or risk calculator, can be recommended before prostate biopsy to improve detection of clinically significant prostate cancer and reduce detection of indolent disease [I, B].
- Multiparametric MRI should be carried out before prostate biopsy; high expertise and quality are essential [I, A].
- In patients with a PI-RADS score of 4-5, prostate biopsy is recommended for histological confirmation [I, A].
- In patients with a PI-RADS score of 3 and high-quality MRI, prostate biopsy can be recommended for histological confirmation, based on PSA-D or presence of prostate cancer risk factors [I, B]. In other cases, biopsy is not mandatory, following shared decision making [I, D].
- In patients with a PI-RADS score of $\leq$2, high-quality MRI and low suspicion for prostate cancer, biopsy is not recommended [I, E].
- Transperineal biopsies are recommended over transrectal US-guided biopsies [I, A].
- Individual reporting of each core biopsy according to location and evaluation in line with ISUP guidelines can be recommended [II, B].

STAGING AND RISK ASSESSMENT

Staging of localised prostate cancer is shown in Figure 1. Localised disease is classified as low, favourable intermediate, unfavourable intermediate, high or very high risk as a guide to prognosis and therapy (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.12.009).[16] Notably, this classification is less applicable to prostate cancer diagnosed via MRI-targeted biopsies and needs to be adapted for current diagnostic pathways. Staging is based on the ninth edition of the Union for International Cancer Control TNM (tumour—node—metastasis) system

(Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.12.009).[17]

MRI provides local staging, can inform surgical technique (e.g. nerve sparing and excision of areas of potential extraprostatic extension) and is used in radiotherapy (RT) planning. Patients with low-risk disease (T1-2a, ISUP grade group 1, PSA $\leq$10 ng/ml) do not require further imaging for staging, but MRI can inform on the risk of clinically significant prostate cancer and help with discussions on active surveillance.[18] Patients with favourable intermediate-risk disease do not require further imaging for staging, unless there is a suspicion of disease underestimation. Patients with ISUP grade group $\geq$3 or high-risk disease should undergo imaging for detection of nodal or metastatic disease. Prostate-specific membrane antigen (PSMA)—positron emission tomography (PET)—computed tomography (CT)[19,20] and possibly whole-body MRI have better accuracy than CT or bone scintigraphy, but they have not been shown to improve clinical outcomes. As the clinical impact of upstaging with PSMA—PET—CT or whole-body MRI compared with conventional imaging is unknown, patients with localised disease on conventional imaging should not be denied radical local treatment solely because metastatic lesions are identified on novel imaging techniques only [i.e. if no correlates are observed on the bone windows or lymph nodes (LNs) of the CT scan].

Genomic and pathology-based signatures have been developed and validated to guide risk assessment and treatment decisions, but they are not yet recommended for clinical practice.[21-23]

Due to the frequent slow progression of localised prostate cancer, life expectancy influences treatment decisions. Estimation of life expectancy, however, is challenging, taking into consideration age, comorbidities and medication, as well as nutritional, cognitive and physical status. Elderly patients may require a specialised geriatric assessment, particularly if they are considered frail based on screening tools such as G8 and Mini-Cog.[24]

Recommendations

- Localised disease should be classified as low, favourable intermediate, unfavourable intermediate, high or very high risk as a guide to prognosis and therapy [III, A].
- MRI can be recommended for local staging before local treatment, if not carried out before biopsy [III, B].
- Patients with unfavourable intermediate-risk, high-risk or very high-risk disease can be staged for metastases using PSMA—PET—CT as it provides the highest accuracy [I, B]. If PSMA—PET is unavailable, whole-body MRI, choline PET—CT or conventional imaging (CT scan of the chest, abdomen and pelvis, as well as bone scintigraphy) can be used [I, B].
- Patients with negative conventional imaging and positive PSMA—PET—CT should still be considered for local treatment [I, B]; multidisciplinary team discussion can be recommended [III, B].
- Life expectancy and frailty should be assessed as part of the initial patient evaluation [III, A].

MANAGEMENT OF LOCALISED DISEASE

There is no single best option for the optimal management of localised prostate cancer.[25] Patients should be informed about the benefits and harms of all treatments within the context of their personal preferences and comorbidities. Given the range of therapies and their side-effects (including sexual dysfunction, infertility and bowel and urinary problems), patients should be offered consultation with both a urologist and a radiation oncologist. Treatment options with curative intent include radical prostatectomy (RP), external beam RT (EBRT) and brachytherapy.

Watchful waiting and active surveillance

Watchful waiting (WW) with delayed hormone therapy upon symptomatic progression is an option for patients who are not suitable for, or are unwilling to undergo, treatment with curative intent.

Active surveillance is a strategy of close monitoring of patients with low-risk disease and selected patients with intermediate-risk disease, typically involving repeat PSA tests, MRI and biopsies, with curative treatment as an option for patients with evidence of disease progression. To date, no clear data exist regarding optimal frequency of follow-up for patients undergoing active surveillance. Moreover, there are no clear data on the assessments that should be carried out at each follow-up visit, criteria for disease progression or triggers to switch to curative treatment. Cancer characteristics must be considered within the context of patient life expectancy and the presence of comorbidities. Active surveillance aims to minimise treatment-related toxicity without compromising cancer control and survival.

RP

Two RCTs have compared RP with WW.[26,27] The Scandinavian Prostate Cancer Group (SPCG) Trial Number 4 evaluated 695 patients from 1989 to 1999, when PSA testing was not routinely carried out; therefore, its findings may not apply to screening-detected cancers.[26] After a median follow-up of 30 years, RP resulted in a 48% lower risk of death from prostate cancer than WW (relative risk 0.52, 95% CI 0.40-0.67), and the number of patients who would need to be treated to avert one death from prostate cancer was six (95% CI 4-10). Patients in the RP group also had lower overall mortality than those in the WW group; however, the benefit of RP over WW was only apparent after long-term follow-up, highlighting that life expectancy is a key component of decision making for radical therapy versus WW.[26] The PIVOT trial recruited 731 North American patients with localised prostate cancer from 1994 to 2002.[27] This population was more representative of patients with PSA screening-detected cancer, but patients had a remarkably high rate of comorbidities. At a median follow-up of 18 years, surgery was associated with lower all-cause mortality compared with observation in patients with clinically localised prostate cancer (relative reduction 8%, corresponding to an absolute reduction of 5.7 percentage points and a mean survival increase of

1 year).[27] The high all-cause mortality rate of ~50% at 10 years reflects the inclusion of patients with significant comorbidities and insufficient baseline life expectancy.[27]

ProtecT was a prospective randomised clinical phase III study comparing treatment with curative intent (RP or RT) with active monitoring (repeat biopsy in patients with a PSA rise of >50% from baseline and no routine use of MRI).[25] The trial recruited 1643 patients with localised prostate cancer between 1999 and 2009, reflective of a PSA screening-detected cohort. After 15 years of follow-up, there was no statistically significant difference in terms of cancer-specific or all-cause mortality rates between the three arms; however, patients in the active monitoring group had a higher metastatic progression rate (9.4%) compared with RP (4.7%) or RT (5.0%).[25] Notably, two-thirds of patients undergoing active monitoring had received radical intervention by 15 years. There were substantial long-term differences in urinary, gastrointestinal (GI) and sexual dysfunction in favour of active monitoring. It is important to note that current active surveillance protocols often use a combination of repeated PSA measurements, DRE, MRI and prostate biopsies. Nevertheless, ProtecT demonstrated that a less intensive follow-up regimen might be sufficient to maintain favourable overall and cancer-specific survival in patients undergoing active surveillance.

RP planning should consider the local tumour extent and location, as well as the risk of LN metastases. Surgery should aim for the highest chance of cancer control and the lowest risk of urinary and sexual side-effects. Margins and nerve sparing should be balanced to achieve both goals. Many techniques and tools are available to achieve these aims.[28]

The role of LN dissection during RP remains controversial. Extended pelvic LN dissection (PLND) provides the highest accuracy of LN staging relative to imaging. Data from two RCTs with short-term follow-up did not show improved biochemical recurrence (BCR)-free survival after extended PLND versus limited PLND.[29,30] An updated analysis of one of these trials with longer follow-up confirmed the absence of improved BCR-free survival but did report improved metastasis-free survival (MFS) in the extended PLND arm [hazard ratio (HR) 0.75, 95% CI 0.64-0.88, $P < 0.001$].[31,32]

RP combined with systemic treatment

The combination of RP with systemic treatments, particularly neoadjuvant therapy, has been evaluated in several RCTs, with a systematic review concluding that neoadjuvant androgen deprivation therapy (ADT) is associated with a reduction in tumour size, downstaging and a reduced rate of positive surgical margins, but no improvement in cancer control.[33] Recent phase II studies explored next-generation hormonal therapies in combination with ADT, demonstrating an effect on downstaging and a higher rate of minimal residual disease in the interventional arm.[34,35] No data are available on short- or mid-term cancer control outcomes. Ongoing phase III trials [e.g. PROTEUS (NCT03767244)] are exploring the same strategy. Currently, no evidence supports the use of perioperative ADT outside of clinical trials.

RT

No survival data have been published from studies evaluating RP versus RT—ADT in high-risk prostate cancer, but the ongoing phase III SPCG-15 trial, which is comparing primary RP with primary RT—ADT for locally advanced disease, will provide evidence in this setting.[36]

The case for adding radical RT to ADT in high-risk localised and locally advanced prostate cancer is based on two phase III RCTs. The SPCG-7 trial included 875 patients who received 3 months of ADT plus a first-generation androgen receptor inhibitor followed by flutamide monotherapy.[37] Patients were then randomised to receive radical RT to the prostate or systemic therapy alone. Radical RT reduced cause-specific mortality (11.9% versus 23.9% with systemic therapy alone, $P < 0.001$) and overall mortality (29.6% versus 39.4%, $P = 0.004$).[37] The National Cancer Institute of Canada/Medical Research Council trial randomised patients with high-risk disease to lifelong ADT alone or ADT—RT.[38] Adding RT improved 7-year survival rates (74% with ADT—RT versus 66% with ADT alone, HR 0.77, 95% CI 0.61-0.98, $P = 0.033$).[38]

For radical prostate RT, dose escalation using intensity-modulated RT, usually with image-guided RT, improves biochemical control with acceptable toxicity. Most studies, however, have not demonstrated MFS or overall survival (OS) benefit,[39] apart from the recent GETUG-AFU 18 trial, which reported improved OS with high-dose RT (80 Gy) combined with long-term hormonal therapy (median OS 77.0 months with 80 Gy versus 65.9 months with 70 Gy, HR 0.61, 95% CI 0.44-0.85, $P = 0.0039$).[40] Multiple phase III studies have shown non-inferiority for moderate hypofractionation compared with schedules over 7-8 weeks, especially in patients with intermediate-risk disease.[41,42] Moderate hypofractionation is more convenient for the patient, more cost-effective for the provider and is associated with equivalent toxicity rates when compared with conventional RT.[43] Stereotactic body RT (SBRT) has been shown to be non-inferior for biochemical control in patients with ISUP grade group 2 intermediate-risk disease, albeit with a slightly higher risk of genitourinary (GU) side-effects.[44] Ten-year follow-up data from the non-inferiority HYPO-RT-PC trial confirmed the safety and efficacy of ultra-hypofractionation compared with standard fractionation for localised disease.[45]

The role of prophylactic pelvic nodal RT is not clear, with trials reporting contrasting results in terms of oncological benefit.[46,47]

In patients with ISUP grade group 2 intermediate-risk disease, the PACE-B trial reported a 5-year BCR-free survival rate of 96% after SBRT without ADT.[44] For patients with primary Gleason score ≥4, concomitant and adjuvant ADT is used alongside RT. ADT has been shown to improve

MFS across risk groups, with the absolute benefit dependent on baseline risk.[48] All patients with high-risk and very high-risk disease should be considered for long-term ADT (18-36 months).[48]

Patients treated with RP for intermediate- or high-risk disease might require post-operative RT (adjuvant and salvage) with or without ADT. Studies have suggested that salvage prostate bed RT is preferred over adjuvant RT.[49-51] Patients with high-risk characteristics benefit from long-term ADT (2 years) alongside prostate bed RT in terms of MFS, but no OS benefit has been reported.[52] The optimal duration of concomitant ADT (6 versus 24 months) in the salvage setting remains a matter of debate and should be individualised based on cancer risk and comorbidities.[53]

Focal ablative therapy

Focal ablative treatments have recently emerged as therapeutic options in localised prostate cancer. These modalities aim to provide equivalent oncological benefits to RP and RT with improved functional outcomes.[54,55] To date, no prospective randomised studies have compared focal ablation with RP or RT; therefore, these alternative options should only be offered within a clinical trial or prospective registry.

An algorithm for the management of low-, intermediate- or high-risk localised prostate cancer is provided in Figure 2.

Recommendations

- WW with delayed ADT for symptomatic progression is recommended for patients who are not suitable for, or are unwilling to undergo, radical treatment or active surveillance [I, A].
- Active surveillance is recommended for patients with low-risk disease [I, A].
- Active surveillance is also recommended for selected patients with favourable intermediate-risk disease (ISUP grade group 2 and minor component of Gleason score 4) [II, A].
- RP or RT (EBRT or brachytherapy) can be recommended for patients with favourable intermediate-risk disease [I, B].
- SBRT is a recommended option for patients with favourable intermediate-risk and ISUP grade group 2 disease [I, A].
- RP or RT (EBRT with or without brachytherapy) can be recommended for patients with unfavourable intermediate-risk disease [I, B].
- Extended PLND can be recommended for accurate LN staging [I, B], although its impact on outcome remains controversial.
- Ultra-hypofractionated RT can be recommended as an option for patients with intermediate-risk disease [I, B].
- Moderate hypofractionation is recommended for most patients with localised disease [I, A].
- Patients receiving radical RT for intermediate-risk disease with unfavourable features (e.g. ISUP grade group 3) should receive short-course ADT for 4-6 months [I, A].
- EBRT with or without brachytherapy can be recommended for high-risk localised or locally advanced [clinical (c) T3-4, N1] prostate cancer [I, B]. These patients should receive long-course ADT (18-36 months) [I, A].
- Patients' health status should be considered when planning the addition and duration of ADT combined with radical RT [II, A].
- RP [I, B] or RP with PLND [III, B] can be recommended for patients with high-risk localised disease within the context of a potentially multimodal approach.
- Primary ADT alone cannot be recommended as initial treatment of non-metastatic disease [I, D].
- Adjuvant post-operative RT after RP cannot generally be recommended [I, D].

MANAGEMENT OF VERY HIGH-RISK AND/OR cN+ DISEASE

Very high-risk or locally advanced prostate cancer is often characterised based on the presence of extra-prostatic tumour growth and/or pelvic LN metastasis. The multi-arm, multi-stage STAMPEDE platform protocol explored treatment options in this patient cohort.[56] Patients presenting with non-metastatic disease on conventional imaging and with very high-risk features (defined as N+ or, if N0, two of: T3 or T4, Gleason sum 8-10 or PSA $\geq$40 ng/ml) were randomised to receive standard of care (SoC) RT to the prostate (with or without RT to pelvic LNs) combined with 3 years of ADT or RT to the prostate (with or without RT to pelvic LNs) combined with 3 years of ADT plus 2 years of abiraterone.[56] The addition of abiraterone significantly improved MFS (HR 0.54, 95% CI 0.43-0.68) and OS (HR 0.63, 95% CI 0.48-0.82).[56]

Patients with metastatic disease on PSMA–PET–CT but non-metastatic disease on conventional imaging might best be managed as patients with very high-risk locally advanced disease. There is currently no level of evidence (LoE; see Methodology) I for adjuvant or neoadjuvant androgen receptor pathway inhibitors (ARPIs) other than abiraterone, or for such treatment intensification in patients undergoing surgery. Surgery in this situation lacks the possibility for treatment intensification with an ARPI and is likely to be followed by further multimodal treatments (RT or hormonal therapy).[57]

An algorithm for the management of very high-risk or cN1 disease is provided in Figure 3.

Recommendations

- EBRT with or without brachytherapy to the prostate (and pelvic nodes if indicated) combined with neoadjuvant and adjuvant ADT (3 years) and abiraterone (2 years) is recommended for patients with very high-risk localised disease or cN1 disease [I, A; abiraterone is not European Medicines Agency (EMA) or Food and Drug Administration (FDA) approved in this setting].

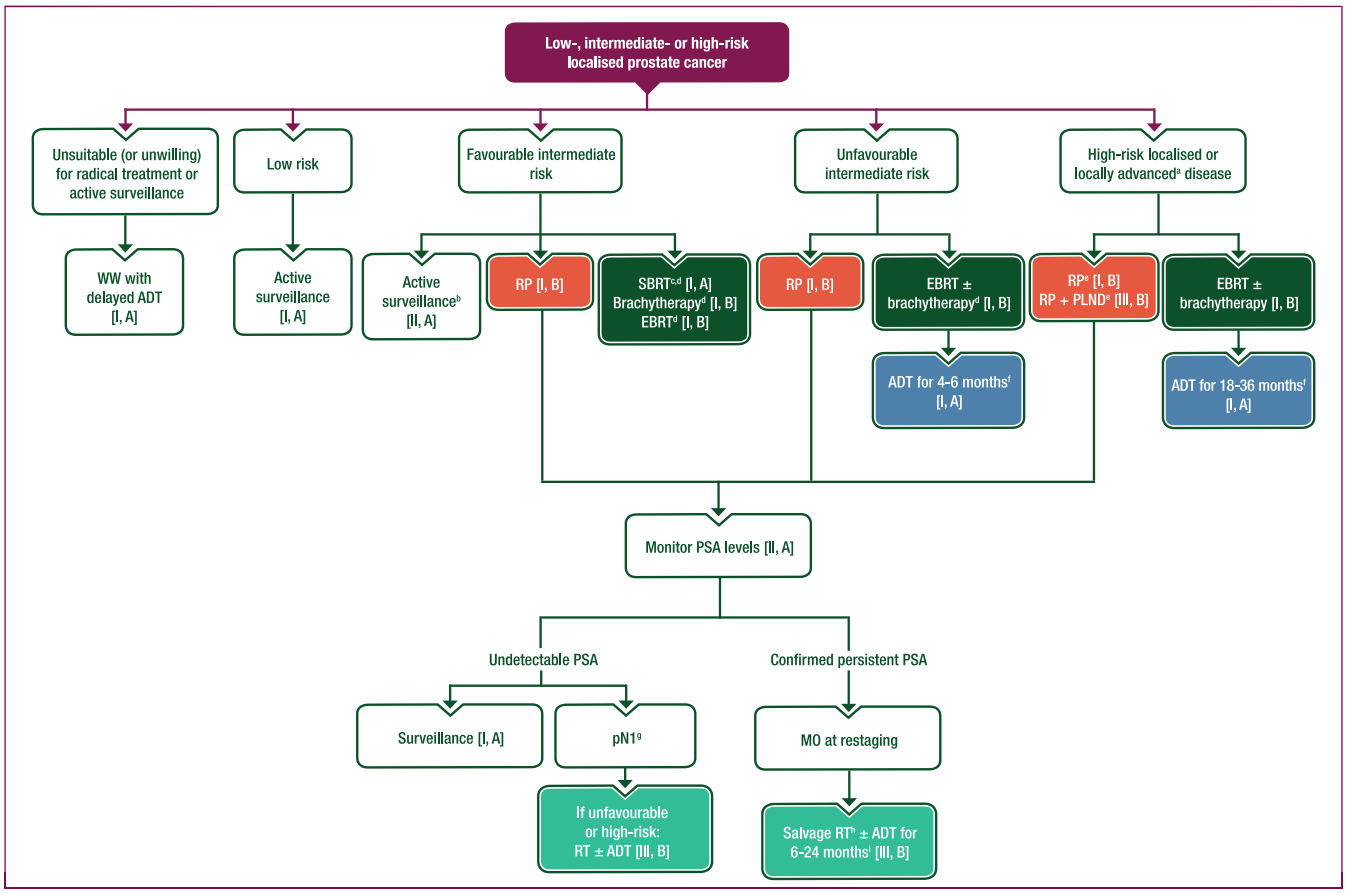

Figure 2. Management of low-, intermediate- or high-risk localised prostate cancer.
Purple: algorithm title; orange: surgery; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
ADT, androgen deprivation therapy; c, clinical; EBRT, external beam RT; ISUP, International Society of Urological Pathology; LN, lymph node; p, pathological; PET, positron emission tomography; PLND, pelvic LN dissection; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy; SBRT, stereotactic body RT; WW, watchful waiting.
[a]Locally advanced disease defined as cT3-4, N1.
[b]Patients with ISUP grade group 2 disease and minor component of Gleason score 4.
[c]Patients with ISUP grade group 2 disease.
[d]Ultra-hypofractionated RT can be recommended as an option for patients with intermediate-risk disease [I, B]. Moderate hypofractionation is recommended for most patients with localised disease [I, A].
[e]Selected patients with high-risk disease within the context of a potentially multimodal approach.
[f]Patients' health status should be considered when planning the addition and duration of ADT combined with radical RT [II, A].
[g]Decisions for additional treatment in patients with pN1 disease and undetectable PSA after surgery can be based on pathology (pathological stage, ISUP grade group, number of positive LNs) and patient preference [III, B].
[h]To prostate bed ± pelvic nodes (if high risk of pelvic nodal recurrence); if PSMA–PET staging is M0 or if PSMA–PET is not available and conventional imaging suggests M0.
[i]Patients with PSA >0.6 ng/ml at salvage RT, nodal metastases, ISUP grade group 4-5 and/or presence of seminal vesicle invasion.

- RP [I, B] or RP with PLND [III, B] can be recommended for selected patients with very high-risk localised disease within the context of a potentially multimodal approach.
- Adjuvant RT with or without ADT may be considered for patients with very high-risk disease and pathological (p)N1 after RP [IV, C].

MANAGEMENT OF pN1 DISEASE

Pathological LN involvement at the time of RP and PLND is an adverse prognostic factor. In a Surveillance, Epidemiology, and End Results (SEER) study of 30 016 patients undergoing RP, of whom 1869 were found to have pN1 disease, 5-year cause-specific mortality was 6.0% for patients with pN1 disease versus 0.8% for patients with pN0 or pNx disease.[58] Five-year cause-specific mortality was 2.4% for those with 1-2 positive LNs and 7.2% for those with ≥3 positive LNs.[58] In patients with pN1 disease, persistently detectable post-operative PSA is associated with poor outcomes. A study of 319 patients with pN1 disease, of which 83 had persistently detectable PSA (>0.1 ng/ml) at 6 weeks, reported an 8-year cause-specific mortality rate of 16% for those with persistently detectable PSA versus 4% for those without.[59]

Treatment options for pN1 disease after RP and PLND include observation (if PSA is undetectable) with treatment upon disease progression, adjuvant ADT and/or adjuvant RT. There is a lack of RCT data in this setting. A randomised trial of 98 patients in the pre-PSA era reported an OS

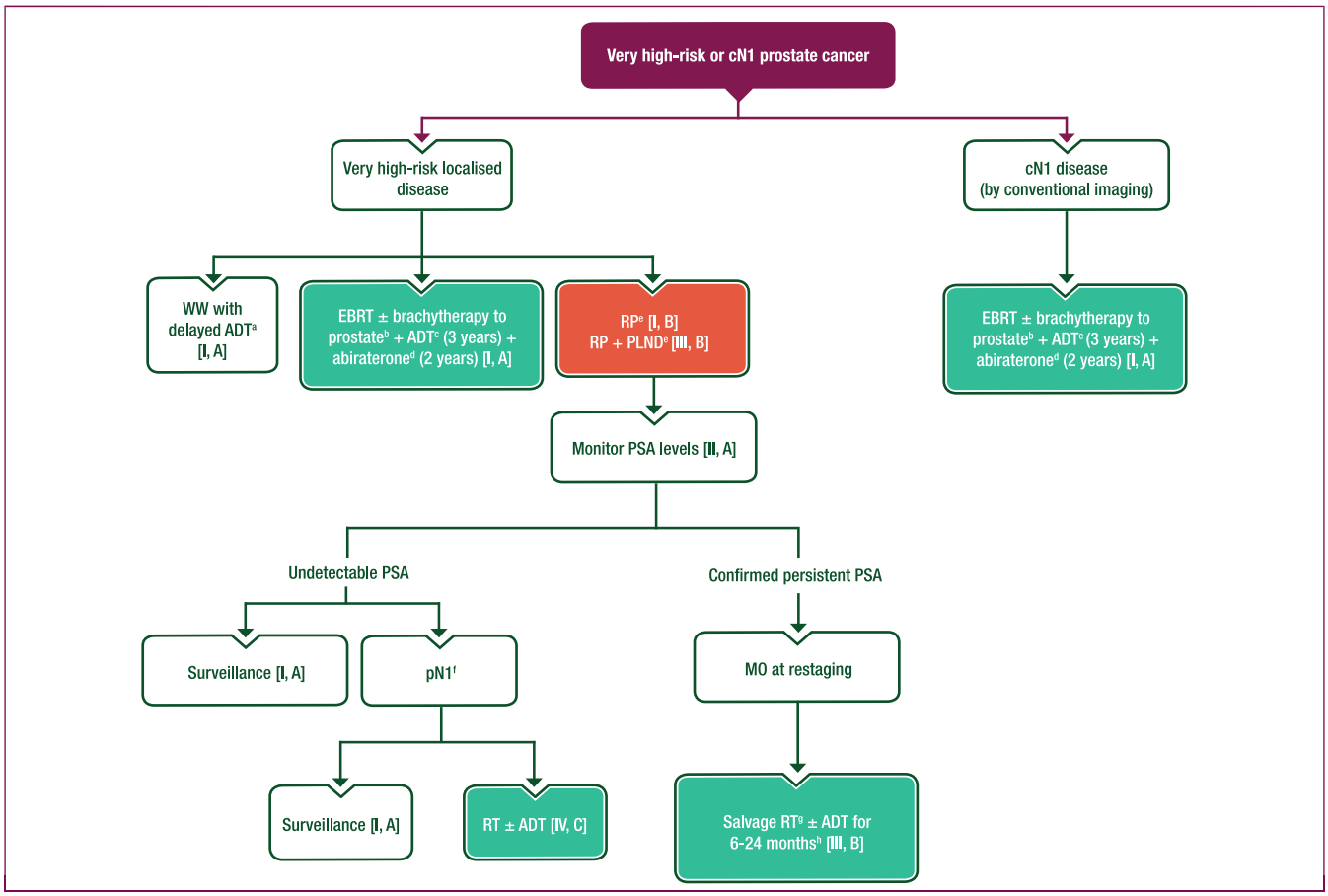

Figure 3. Management of very high-risk or cN1 prostate cancer.
Purple: algorithm title; orange: surgery; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
ADT, androgen deprivation therapy; c, clinical; EBRT, external beam RT; EMA, European Medicines Agency; FDA, Food and Drug Administration; ISUP, International Society of Urological Pathology; LN, lymph node; p, pathological; PET, positron emission tomography; PLND, pelvic LN dissection; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy; WW, watchful waiting.
[a]If patient is not suitable for (or unwilling to have) radical treatment.
[b]Pelvic nodal RT can be considered in patients at high risk of pelvic nodal recurrence [II, B].
[c]Patients' health status should be considered when planning the addition and duration of ADT combined with radical RT [II, A].
[d]Not EMA or FDA approved in this setting.
[e]Selected patients with very high-risk disease within the context of a potentially multimodal approach.
[f]Decisions for additional treatment in patients with pN1 disease and undetectable PSA after surgery can be based on pathology (pathological stage, ISUP grade group, number of positive LNs) and patient preference [III, B].
[g]To prostate bed ± pelvic nodes (if high risk of pelvic nodal recurrence); if PSMA–PET staging is M0 or if PSMA–PET is not available and conventional imaging suggests M0.
[h]Patients with PSA >0.6 ng/ml at salvage RT, nodal metastases, ISUP grade group 4-5 and/or presence of seminal vesicle invasion.

benefit with immediate versus deferred ADT,[60] but this is of uncertain relevance to contemporary practice. Randomised trials of adjuvant RT have included very few patients with pN1 disease. A retrospective study reported that adjuvant RT was associated with improved disease outcomes in patients with adverse pathology,[61] but this does not amount to high-level evidence.

Recommendations

- Decisions for additional treatment in patients with pN1 disease and undetectable PSA after surgery can be based on pathology (pathological stage, ISUP grade group, number of positive LNs) and patient preference [III, B].
- Adjuvant RT (with or without ADT) can be considered in patients with unfavourable characteristics [III, B].

MANAGEMENT OF PERSISTENT PSA AFTER RP

Patients with persistent PSA after RP (PSA >0.1 ng/ml 6-9 weeks after surgery) should have repeat staging to determine the possibility of salvage RT.[62] Whenever possible, PSMA-based imaging should be used.[63] Conventional imaging with CT or MRI and bone scintigraphy has a low diagnostic yield at low PSA levels. The role of salvage RT and metastasis-directed therapy is uncertain in patients with distant metastases; these cases should be discussed in a multidisciplinary setting and/or included in clinical trials. In the absence of distant metastases, salvage RT may be

used, and the addition of ADT should be considered, although there is a lack of data in this clinical scenario. Based on results from the RADICALS-HD study, there is controversy around the dose and duration of ADT if this strategy is used for patients with PSA elevations following a period of undetectable PSA after RP.[52,53] It is unclear how these data can be extrapolated to the setting of persistent PSA. Patients with persistent PSA after RP are considered to be at higher risk of failure if RT is given without ADT.[64]

Recommendations

- Surveillance is recommended for patients with undetectable PSA after RP [I, A].
- Patients with confirmed persistent PSA >0.1 ng/ml after RP can be restaged with PSMA–PET–CT if available [III, B].
- If PSMA–PET–CT is not available, conventional imaging can be considered if not done before surgery and if there are high-risk post-operative features (e.g. LN metastases, ISUP grade group 4-5 and/or presence of seminal vesicle invasion) [III, B].
- Salvage RT can be recommended if PSMA–PET staging is M0 or if PSMA–PET is not available and conventional imaging suggests M0 [III, B].
- Pelvic nodal RT can be recommended for patients at high risk of pelvic nodal recurrence [II, B].
- The addition of ADT (6-24 months) can be recommended for patients with higher PSA at salvage RT (>0.6 ng/ml), nodal metastases, ISUP grade group 4-5 and/or presence of seminal vesicle invasion [III, B].

MANAGEMENT OF BCR AFTER LOCAL TREATMENT

Follow-up and BCR

Patients are monitored after local treatment of oncological, functional and toxicity purposes. PSA tests should be carried out on a regular basis, with their frequency reflecting the risk of recurrence, which is highest during the first 3 years after surgery.[65] There are no prospective data providing information on the optimal PSA testing regimen, but a reasonable schedule may be every 6 months during the first 3 years and annually beyond that. For patients undergoing radical RT and ADT, testosterone recovery needs to be monitored together with PSA, and closer follow-up might be warranted during this process (e.g. every 6 months). Late recurrences are observed; therefore, long-term follow-up seems to be warranted, especially as the PSA test is risk free. After local treatment, BCR is defined as a PSA rise in the absence of disease on imaging. After RT, BCR is defined by following the Phoenix criteria of PSA nadir +2 ng/ml.[66] After RP, BCR is defined as a rising PSA level that is confirmed by a second rise, after having been non-detectable (<0.1 ng/ml) after RP.[67] These definitions should, however, primarily be viewed as a means of standardising reporting of outcomes and not as hard limits for triggering action, having been defined arbitrarily rather than based on interaction with outcomes.

Risk stratification for BCR

BCR remains a heterogeneous disease scenario with some patients not progressing to metastatic disease even after long-term follow-up, and others progressing to metastases and death.[68] For that reason, life expectancy and comorbidities are equally important as cancer characteristics when managing BCR. Recurrence may be local (prostatic bed after RP or prostate after RT), locoregional (pelvic LNs), distant (bones, viscera) or combined. Several risk factors allow evaluation of mortality risk in patients with BCR. A short PSA doubling time (<6-12 months) and initial ISUP grade group 4-5 are associated with increased prostate cancer-specific mortality after RP,[69] whereas after RT, early development of BCR (<18 months) and initial ISUP grade group 4-5 are linked to increased mortality.[70] Genomic classifiers are an additional option to risk stratify patients with BCR to treatment or surveillance.[71] Patients without these risk characteristics might have more favourable long-term disease outcomes[70] and may not require salvage treatment.

Restaging in BCR

Differentiation of locoregional from systemic disease in patients with BCR based on conventional imaging (bone scintigraphy, CT) is challenging, as sensitivity for detecting nodal or metastatic recurrences is poor at low PSA levels. PSMA–PET imaging is replacing conventional imaging based on its superior sensitivity and specificity.[72,73] After RP, MRI lacks sensitivity in detecting local recurrence at low or very low PSA ranges and cannot be recommended.[74] After RT, MRI has good sensitivity in early BCR to detect local, intraprostatic recurrence and can help guide biopsy cores to histologically confirm local recurrence.[74] No trial data support the omission of local salvage RT in the absence of an imaging-detected local recurrence.

Only one trial has reported that the detection of recurrence and a subsequent treatment change improves outcomes. The EMPIRE-1 study was a single-centre, open-label, phase II-III RCT, in which patients with detectable PSA after RP and negative conventional imaging (no extrapelvic or bone findings) were randomly assigned (1 : 1) to RT directed by conventional imaging alone or by conventional imaging plus ^{18}F-fluciclovine-PET–CT.[75] Three-year event-free survival was 63.0% (95% CI 49.2% to 74.0%) in the conventional imaging group versus 75.5% (95% CI 62.5% to 84.6%) with ^{18}F-fluciclovine-PET–CT (95% CI 4.3% to 20.8%, $P = 0.0028$). Distant failure-free survival was 51.2% with conventional imaging versus 75.5% with ^{18}F-fluciclovine-PET–CT (95% CI 15.6% to 33.0%, $P < 0.0001$).[75] It is notable that patients with extrapelvic or skeletal disease on

^{18}F-fluciclovine-PET—CT were excluded from analysis in the PET group, resulting in inflated positive outcomes in this arm.[75]

Nodal recurrences based on novel imaging after maximal local therapy

Several randomised phase II trials have evaluated RT options for PET—CT-detected nodal or metastatic recurrences.[76-78] The PEACE V-STORM trial randomised patients with PET-detected nodal recurrences to either a metastasis-directed approach or whole pelvis RT (RT of all pelvic LNs) and showed that whole pelvis RT resulted in superior BCR-free survival (HR 0.62, 80% CI 0.48-0.80, $P = 0.014$) and MFS [HR 0.62, 80% CI 0.44-0.86, $P = 0.063$ (statistically significant)] at 4 years.[79] Based on these results, elective nodal RT with inclusion of the prostate bed, if not previously treated, provides the best oncological outcomes for patients with PET-detected nodal recurrences. No prospective trials of surgical salvage LN dissection have been published.

Observation versus systemic therapy for BCR

The median time from detection of BCR to developing metastases on conventional imaging is 8 years, and the median time from metastasis to death is another 5 years.[68] The TOAD[80] and ELAAT[81] studies compared early versus deferred ADT in patients with PSA failure after local therapy. The reasons to start ADT were the development of symptoms or metastases on conventional imaging or PSA doubling time decreasing to 6 months. Pooled analysis of the two studies reported no OS benefit with early ADT (HR 0.75, 95% CI 0.40-1.41, $P = 0.37$).[82] Early ADT adversely affected quality of life in terms of sexual activity and hot flushes.

Intermittent versus continuous ADT was studied in a randomised trial of 1386 patients with a PSA level of >3.0 ng/ml at relapse >1 year after radical RT.[81] Intermittent ADT had a more favourable toxicity profile with no difference in OS (HR 1.02, 95% CI 0.86-1.21).[81] This emphasises that the timing of systemic therapy should be balanced against possible side-effects, life expectancy and comorbidities. Risk factors that might help risk stratify patients are PSA doubling time, ISUP grade group and time interval from local treatment to BCR.

The phase III EMBARK study randomised 1068 patients with high-risk BCR (1 : 1: 1) to enzalutamide daily plus leuprolide every 12 weeks, placebo plus leuprolide or enzalutamide monotherapy.[83] High-risk BCR was defined by a PSA doubling time of ≤9 months and PSA ≥2 ng/ml above nadir after RT or ≥1 ng/ml after RP with or without post-operative RT. Treatment could be interrupted after 9 months if PSA reduced to <0.2 ng/ml, with reinitiation at ≥2.0 ng/ml (prior RP) or 5.0 ng/ml (prior RT). The 5-year MFS rate was improved with enzalutamide—leuprolide versus placebo—leuprolide (HR 0.42, 95% CI 0.30-0.61, $P < 0.001$).[83] The 8-year OS rate was also higher with enzalutamide—leuprolide versus placebo—leuprolide (HR 0.60, 95% CI 0.44-0.80, $P < 0.001$).[84] MFS was also improved with enzalutamide monotherapy compared with placebo—leuprolide (HR 0.63, 95% CI 0.46-0.87, $P = 0.005$),[83] but there was no significant OS benefit.[84] AE profiles were different between the groups, with notable gynaecomastia with enzalutamide monotherapy.[83]

Adjuvant versus salvage RT and other local salvage options

Post-operative RT following RP may be given as adjuvant RT (undetectable post-operative PSA) or salvage RT (persistent or rising PSA). Four RCTs have investigated adjuvant RT compared with observation;[85-88] all demonstrated improved biochemical control with adjuvant RT, but no consistent OS benefit. More recently, RADICALS-RT,[49] RAVES[50] and GETUG-AFU 17[51] have compared adjuvant RT versus observation with early salvage RT upon PSA failure. These trials were combined in the ARTISTIC meta-analysis, which concluded that adjuvant RT was associated with more harm (increased bladder and bowel toxicity) and no proven benefit in terms of progression-free survival (PFS).[89] Salvage RT should be given early; outcomes are more favourable if it is initiated when PSA is <0.5 ng/ml.[70] Of note, in RADICALS-RT, RAVES and GETUG-AFU 17, salvage RT was started at PSA ≥0.1 ng/ml or three consecutive rising PSA results,[49] PSA ≥0.2 ng/ml[50] and PSA ≥0.1 ng/ml confirmed after 4 weeks,[51] respectively (i.e. lower than 0.5 ng/ml). A recent analysis based on individual patient data from GETUG-AFU 16, NRG/RTOG-9601 and a subgroup of EORTC-22911 reported that three prognostic groups can be identified based on PSA ≥0.5 ng/ml at start of salvage RT, Gleason score ≥8 and negative margin status, where high risk is two or three of these risk factors, intermediate risk is one risk factor and low risk is zero risk factors.[90]

Two trials have compared salvage RT versus salvage RT plus 6 months of ADT, reporting improvements in MFS and PFS with the addition of ADT, but no OS benefit.[91,92] The RTOG 9601 study demonstrated a lower rate of prostate cancer death (HR 0.77, 95% CI 0.59-0.99, $P = 0.04$) and improved OS (HR 0.49, 95% CI 0.32-0.74, $P < 0.001$) with salvage RT plus 24 months of bicalutamide versus salvage RT alone.[93] *Post hoc* subgroup analyses indicated that patients with a pre-RT PSA >0.7 ng/ml, Gleason score 8-10 and positive margins derived the greatest benefit from the addition of bicalutamide.[93]

The RADICALS-HD trial evaluated 6 months or 24 months of ADT in addition to post-operative RT, combining adjuvant RT and salvage RT in the study cohorts. One analysis compared 6 months of ADT with no ADT and reported no MFS benefit.[53] A second analysis evaluated 6 months versus 24 months of ADT and reported a 10-year MFS benefit with 24 months of ADT (HR 0.773, 95% CI 0.612-0.975, $P = 0.029$).[52] The most pronounced effect was observed in patients with PSA >0.5 ng/ml at the time of RT

and in patients with a Charlson Comorbidity Index of 0. Patients with lower-risk disease seem to derive little benefit from adding ADT, whereas patients with higher-risk disease, if being offered ADT, should receive 24 months of treatment. It should be noted, however, that groupings were not predefined and were determined by clinical preference. Decisions about adding ADT and the length of treatment should incorporate patient preferences and comorbidities.

Histological proof of local recurrence by biopsy is needed before local salvage treatment after initial organ-sparing treatment, if MRI or PSMA—PET shows suspicion of local recurrence. Local salvage treatment with a curative approach can be offered to well-informed patients. Treatment options are salvage RP, SBRT or salvage ablation [e.g. high intensity focused ultrasound (HIFU), cryotherapy, laser therapy].[94] In a recent meta-analysis of 28 studies, RFS rates were 84.0%, 69.0%, 58.0% and 45% after brachytherapy, EBRT, cryotherapy and HIFU, respectively.[95] After salvage RP, RFS was 75%-78.5% at a median follow-up of 18-35 months. No prospective RCTs have compared these treatment options, and any local salvage treatment is associated with an increased risk of treatment-related GU and GI toxicity.[94]

An algorithm for the treatment of patients with BCR is shown in Figure 4.

Recommendations

- Following RP, serum PSA levels should be monitored [II, A].
- In case of BCR after RP, PSMA—PET—CT can be recommended before pelvic salvage treatment [II, B]. In case of BCR after RT, both PSMA—PET—CT and MRI can be recommended, especially if local salvage treatment is being considered [II, B].
- Surveillance can be recommended for patients with BCR who are at low risk of metastatic progression [III, B].
- Salvage RT can be recommended in the event of PSA failure if there is a risk of metastatic progression (PSA doubling time $<$6-12 months after RP) [III, B].
- Salvage RT should start early (ideally PSA $\sim$0.2 ng/ml but also taking into account other factors such as PSA doubling time, pathology, surgical margins and time from surgery) [I, A].
- Pelvic nodal RT may be considered for patients undergoing salvage RT to the prostate bed [I, C].
- For patients undergoing salvage RT, concomitant ADT for 6-24 months or bicalutamide 150 mg daily for 2 years can be recommended [I, B].
  - Long-term ADT can be recommended for patients at high risk of progression [I, B] and short-term or no ADT can be recommended for patients at low risk of progression [I, B].
  - Early ADT alone cannot be recommended for patients with low-risk BCR and no indication for local salvage treatment [II, D].
  - Intermittent ADT can be recommended for patients with BCR and absence of metastatic disease on conventional imaging who achieve a deep PSA response under ADT [I, B]. The optimal regimen for intermittent ADT is unknown.
- For patients with high-risk BCR (short PSA doubling time, ISUP grade group 4-5, symptomatic local disease or proven metastases), immediate ADT can be recommended [II, B].
- Salvage ablation or salvage RP can also be recommended for patients with high-risk BCR [III, B].
- ADT—enzalutamide is recommended for patients with BCR and high-risk features who are not candidates for radical salvage treatment (M0 on conventional imaging, PSA doubling time $<$9 months, PSA $>$1 ng/ml after RP or PSA $\geq$2 ng/ml above nadir after RT) [I, A; ESMO-Magnitude of Clinical Benefit Scale (MCBS) v2.0 score: 2 but associated with an increased risk of toxicity].
  - In patients refusing ADT, enzalutamide monotherapy can be recommended [I, B; ESMO-MCBS v2.0 score: 3].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/guidelines/esmo-guidelines-methodology). All recommendations provided are based on current scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated by ordering these options according to: LoE and grade of recommendation (GoR); where equal, by ESMO-MCBS score; where equal, by alphabetical order. The relevant literature has been selected by the expert authors. ESMO-MCBS v2.0[96] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/guidelines/esmo-mcbs). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. LoEs and GoRs have been applied using the system shown in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.12.009.[97] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including Express Updates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/esmo-clinical-practice-guideline-local-and-locoregional-prostate-cancer.

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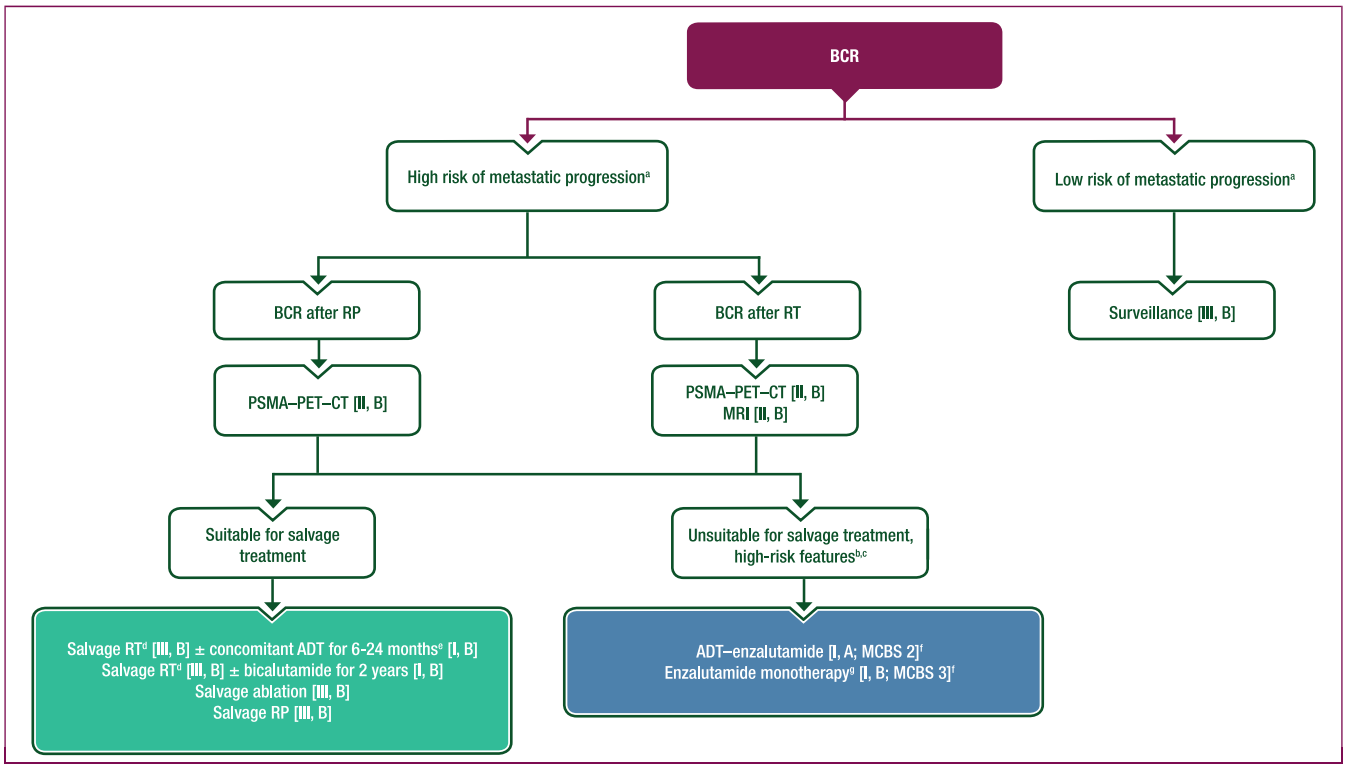

Figure 4. Management of patients with BCR.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
ADT, androgen deprivation therapy; BCR, biochemical recurrence; CT, computed tomography; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy.
[a]High risk: PSA doubling time <6-12 months after RP; low risk: all others.
[b]M0 on conventional imaging, PSA doubling time <9 months, PSA >1 ng/ml after RP or PSA ≥2 ng/ml above nadir after RT.
[c]For patients with high-risk BCR, immediate ADT can be recommended [II, B].
[d]Salvage RT should start early (ideally PSA ∼0.2 ng/ml but also taking into account other factors such as PSA doubling time, pathology, surgical margins and time from surgery) [I, A]. Pelvic nodal RT may be considered for patients undergoing salvage RT to the prostate bed [I, C].
[e]Long-term ADT can be recommended for patients at high risk of progression [I, B] and short-term or no ADT can be recommended for patients at low risk of progression [I, B]; intermittent ADT can be recommended for patients with BCR and absence of metastatic disease on conventional imaging who achieve a deep PSA response under ADT [I, B].
[f]ESMO-MCBS v2.0[96] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[g]Patients refusing ADT.

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