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Review Article

Post-prostatectomy radiation therapy: Updated guidelines of the Australian and New Zealand Radiation Oncology Genito-Urinary Group (FROGG)

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ABSTRACT

Over the past few years, a number of randomised controlled trials have been published addressing the management of patients with biochemical recurrence of prostate cancer post-prostatectomy. The trials sought to answer crucial questions regarding the optimal timing, prescribed dose and fractionation of post-prostatectomy radiation therapy (PPRT), as well as identifying the role for androgen deprivation (ADT) and elective pelvic lymph node irradiation. At the same time the use of novel imaging techniques such as PSMA-PET-CT scan and multi-parametric MRI of the pelvis, has increased. The Australian and New Zealand Faculty of Radiation Oncology Genito-Urinary Group (FROGG) convened a conference in September 2022 to review the latest literature and update its recommendations. This conference was attended by Australian, New Zealand and International delegates with presentations being delivered by key opinion leaders in urology, radiation oncology, medical oncology, radiation therapy and diagnostic imaging. Unresolved issues were reviewed by the FROGG working party until consensus was reached. These recommendations cover the role of PPRT, ADT and elective

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pelvic lymph node irradiation. Technical aspects of radiation therapy, such as clinical target volume definitions and planning techniques, which have been in place since 2008, were also updated.

Background

The management of recurrent prostate cancer after definitive surgery is complex and needs to be regularly updated with contemporary data. While radiation therapy (RT) provides the only known curative treatment option in patients who experience biochemical recurrence following radical prostatectomy, there are numerous variables to consider in order to develop an appropriate management plan. Recently, three large randomised controlled trials and a pre-planned *meta*-analysis have sought to determine the optimal timing of post-prostatectomy radiation therapy (PPRT)[1–4]. There have also been prospective trials assessing the additional role for elective pelvic lymph node RT and androgen deprivation therapy (ADT). Prostate specific membrane antigen positron emission tomography (PSMA-PET) and multi-parametric MRI, have increased the specificity and sensitivity in detecting recurrent disease, potentially influencing pre-treatment decision making and the delineation of target volumes. Finally, improvements in RT planning and delivery have resulted in more accurate and conformal treatments which result in improved target coverage and reduced dose to normal tissue organs at risk (OARs).

In order to provide guidance on the contemporary investigation and management of recurrent prostate cancer after prostatectomy, a set of recommendations was developed by the Australian and New Zealand Faculty of Radiation Oncology Genito-Urinary Group (FROGG). These recommendations are an update to the previously published FROGG guidelines from 2008 and 2018[5,6].

Materials and methods

A working party of FROGG members reviewed the literature, appraised the current evidence, and drafted an initial set of recommendations and CTV voluming guidelines. The proposed guidelines were circulated to members of a selected expert panel comprising 13 specialist genitourinary radiation oncologists, one specialist genitourinary clinical oncologist and one urologist for feedback These draft guidelines were presented at a three-day workshop (08/09/2022–10/09/2022) attended by eighty-nine specialists in radiation oncology, urology, medical oncology, radiation therapy, radiology, nuclear medicine and medical physics from Australia and New Zealand. Selected international and local expert speakers presented data on topics relevant to PPRT prior to the presentation of the recommendations.

Following feedback at the meeting, the proposed guidelines were adjusted by the working group and reviewed by the expert panel. Unresolved issues were then referred back to the working party and recommendations, including the incorporation of contemporaneous trials published during this process, re-circulated to the FROGG committee and expert panel for final comment before the finalised recommendations were collated and incorporated into these guidelines.

Results and discussion

Definitions of adjuvant and salvage radiation therapy

A definition of both adjuvant and salvage RT is provided to ensure consistency in the reporting and comparison of outcomes between these treatment approaches. These definitions are not intended to provide guidance on a threshold for RT delivery, nor are they meant to define post-prostatectomy biochemical recurrence. While the ASTRO/AUA defines adjuvant RT (ART) as RT delivered post prostatectomy to patients with an undetectable serum prostate-specific antigen (PSA) level considered at high risk of prostate cancer recurrence[7], the widespread use of ultrasensitive PSA assays necessitates a practical cut off value below which the PSA is considered “undetectable”. We recommend that ART be defined as RT delivered within 6 months post-prostatectomy in patients with PSA < 0.10 ng/mL, if the PSA is not rising. Salvage radiation therapy (SRT) is therefore defined as RT delivered when the PSA is ≥ 0.10 ng/mL or is any magnitude and rising.

Role for adjuvant radiation therapy

Three randomised controlled trials (RCTs) – RAVES, RADICALS-RT and GETUG-AFU 17, as well as the prospectively planned ARTISTIC *meta*-analysis, have been published since the last FROGG guidelines on the management of recurrent prostate cancer were published in 2018 [1–4,6]. These trials compared the efficacy and safety of ART versus observation and early SRT at the time of PSA progression for patients with high risk features. Initiation of early SRT was triggered at a PSA of 0.20 ng/mL in RAVES, 0.20 ng/mL and rising in GETUG-AFU 17 and at either two consecutive rising PSA levels and a PSA of greater than 0.1 ng/ml or three consecutive rising PSA levels in RADICALS-RT. Eligibility criteria were similar across the trials although not identical. RAVES enrolled patients with pT2 disease and positive surgical margins as well as those with pathological extracapsular extension or seminal vesicle invasion(pT3a/b), GETUG-AFU 17 only enrolled patients with pT3a-pT4a (bladder neck involvement only) disease and positive surgical margins, while RADICALS RT enrolled patients with one or more of positive margins, pT3a-pT4 disease or Gleason score of 7–10.

In the *meta*-analysis, 1075 patients were randomly assigned to ART and 1078 to early SRT, the majority of whom had Gleason 7 disease (77.6 %). Median follow up ranged from 60 to 78 months. At the time of analysis, 39.1 % of patients randomised to early SRT had received postoperative RT. At 5 years the proportion of patients free of biochemical progression was high (87–94 %) and there was no significant difference in event-free survival (EFS) between ART and early SRT, with a hazard ratio (HR) of 0.95 (95 % CI 0.75 to 1.21, $P = 0.70$) and only 1 % absolute difference (95 % CI −2% to 3 %) between the treatment arms. Results were broadly consistent across the trials (heterogeneity $p = 0.18$; inconsistency $I^2 = 42$ %) and results from a random effects model were very similar (HR 0.89, 95 % CI 0.62 to 1.27; $p = 0.52$). Patients were stratified according to a number of prespecified subgroups which included pre-surgical PSA, Gleason score, seminal vesicle invasion, surgical margins and CAPRA-S risk groups and there was no evidence of any significant variation in the effect of ART on EFS across any of these subgroups. However, it should be noted that there were a relatively small number of patients with very high risk features such as Gleason score ≥ 8 (15 % of patients) and pT4 disease (0.8 % of patients).

As 60.9 % of patients did not receive any RT at all, both acute and late toxicity were significantly reduced in the SRT arm when compared to ART. RAVES reported significantly higher acute grade 2 or worse genitourinary toxicity in the ART group (70 % versus 54 %, OR 0.34, 95 % CI 0.17–0.68; $p = 0.0022$) with similar results reported in GETUG-AFU 17 (27 % versus 7 %, $p < 0.0001$), and with the additional finding of significantly worse erectile dysfunction (36 % versus 13 %, $p < 0.0001$). In the RADICALS-RT cohort there was significantly worse self reported urinary incontinence at one year in the ART group as well as significantly increased rates of both early and late grade 1–2 diarrhoea and proctitis as well as grade 1–3 haematuria and urethral stricture.

The results of these three trials suggest a policy of close observation followed by early SRT at biochemical recurrence results in equivalent disease outcomes when compared to ART while sparing, or postponing, RT and its potential toxicities in a significant proportion of patients.

Table 1
Role of adjuvant radiation therapy.

Definition: Adjuvant radiation therapy is radiation therapy delivered within 6 months post-prostatectomy in patients with PSA < 0.10 ng/mL and not rising.		
Who is likely to benefit from adjuvant radiation therapy following a radical prostatectomy?	Level of evidence(91)	References
1.1. For the majority of patients, early salvage radiation therapy is preferred to adjuvant radiation therapy.	1	[1–4]
1.2. Adjuvant radiation therapy does not appear to improve event-free survival in men with localised or locally advanced prostate cancer (pN0/Nx) when compared to early salvage radiation therapy.	1	[1–4]
1.3. Adjuvant radiation therapy increases the risk of urinary and bowel toxicity when compared to a policy of early salvage radiation therapy.	1	[1–4]
1.4. In patients found to have pathological lymph node involvement following radical prostatectomy, the optimal timing of treatment is unknown, and there may be a benefit to adjuvant radiation therapy when compared to early salvage radiation therapy.	3	[8,10,12,92]

Table 2
Role of salvage radiation therapy.

Definition: Salvage radiation therapy is radiation therapy delivered post-prostatectomy in the setting of a PSA ≥ 0.10 ng/mL or rising PSA of any magnitude.		
Who is likely to benefit from salvage radiation therapy following a radical prostatectomy?	Level of evidence(91)	References
2.1. Patients with PSA persistence, recurrence or local clinical failure following prostatectomy should be referred early (i.e. prior to the PSA exceeding 0.2 ng/mL) to a radiation oncologist for a discussion regarding salvage radiation therapy.	5	[6,13,14]
2.2. Earlier delivery of salvage radiation therapy, even at PSA 0.1–0.2 ng/mL, is associated with improved biochemical control and freedom from distant metastases	2	[6,13,14,17]
2.3. There is diminishing, but ongoing, benefit from salvage radiation therapy as PSA levels rise.	2	[6,13,14]
2.4. Selected patients may be more suitable for observation rather than early salvage treatment (e.g., elderly patients with long disease-free interval, slow PSA doubling time, low Gleason score and/or significant medical comorbidities).	4	[17–19]

Therefore we recommend that early SRT be the preferred treatment approach in the majority of patients (Table 1).

One caveat to the above is that none of these trials enrolled a significant number of patients with pathological lymph node involvement (3 % of patients enrolled) and so the optimal management strategy for these patients remains unknown. Retrospective, non-randomised evidence from a number of studies suggests that disease specific mortality and overall survival may be improved with ART and ADT in pathologically node positive disease[8–12]. Most recently, Tilki et al., demonstrated that, when compared to early SRT (with RT commenced at a median PSA of 0.30 ng/mL (IQR: 0.20–0.59)), ART was associated with a significant improvement in all cause mortality risk, an improvement which increased in magnitude with each additional positive pelvic lymph node but was only significant in patients with 4 or more positive nodes[8]. Therefore, in patients with pathologically involved lymph nodes, particularly those with other high risk features or multiple involved nodes, it is reasonable to consider ART.

Role for salvage radiation therapy

The ARTISTIC *meta*-analysis demonstrated high rates of biochemical progression free survival (PFS) at 5 years (87–94 %) for patients treated with early SRT[4]. The importance of early delivery of SRT in attaining optimal outcomes, as stipulated in these trials, has a significant body of retrospective evidence to support it. A systematic review of 41 studies including 5597 patients by King et al., showed an average loss of 2.6 % in biochemical recurrence-free survival for every incremental 0.1 ng/mL rise in PSA at time of SRT (95 % CI 2.2–3.1 %)[13]. An updated multi-institutional retrospective study of 2460 patients by Tendulkar et al., which included patients treated with SRT at PSA ≤ 0.2 ng/mL, demonstrated that SRT delivered at the lowest detectable PSA of 0.01–0.2 ng/mL resulted in 5 year freedom from biochemical failure (FFBF) of 71 %. This study also showed that increasing pre-salvage RT PSA was associated with decreasing FFBF and increasing rates of distant metastases[14], a result which does not appear to be accounted for by lead time bias[15]. While these two studies demonstrate that SRT is most effective when delivered at low PSA levels, the study by Tendulkar et al., did include patients with very high risk features (Gleason 9–10 disease and PSA > 2.0 ng/mL) and reported 5 year FFBF of 26 % in this poor prognosis cohort, suggesting that any patient with a persistently rising PSA post-prostatectomy may benefit from SRT[14].

We therefore recommend that patients with a life expectancy of more than 10 years who develop PSA persistence, recurrence or local clinical failure following prostatectomy be referred early to a radiation oncologist (i.e. prior to the PSA exceeding 0.2 ng/mL) for a discussion regarding salvage treatment (Table 2). This recommendation is consistent with ASTRO-AUA guidelines which recommend SRT be initiated at "the earliest sign of PSA recurrence" as well as with ESTRO-EAU-SIOG which emphasize the importance of commencing SRT early, defined as a pre-salvage PSA of ≤ 0.4 ng/mL[16,17].

While the recommendation is that all patients meeting these criteria are referred to a Radiation Oncologist for an opinion, it is important to note that there will be a subset of patients with biochemically recurrent prostate cancer who will not die of their disease and may not develop further clinical progression during their lifetime. An exploratory systematic review found that patients with pathological grade group 1–2 disease and a PSA doubling time > 1 year had a significantly lower risk of clinical progression when compared to others[18]. This result was externally validated using a large retrospective institutional database leading to the recommendation for such patients to be classified as "EAU low-risk BCR" in the latest EAU guidelines[17–19]. It is therefore important that the following features be taken into account when discussing SRT with patients, especially in elderly patients with significant medical comorbidities: Grade group 1–2 disease, long PSA doubling times and protracted disease free interval from surgery to biochemical failure.

Role for imaging investigations

Conventional imaging investigations such as computed tomography (CT) and whole body bone scan are of limited value in asymptomatic patients due to insufficient sensitivity at low PSA levels[20–22]. We recommend against routinely performing conventional imaging in asymptomatic patients with a PSA < 10 ng/mL. This is consistent with previous FROGG guidelines, as well as with European Association of Urology (EAU) and ASTRO/AUA guidelines[6,16,17].

The use and availability of PSMA-PET/CT scanning has markedly increased in recent years. PSMA-PET provides a more sensitive and highly specific modality for detecting recurrent disease post prostatectomy, especially at low PSA values. A *meta*-analysis of 37 studies by Perera et al., reported detection rates using Gallium-68 PSMA-PET in the recurrent setting of 33 % at PSA 0–0.19 ng/mL, 45 % at 0.2–0.49 ng/mL, 59 % at 0.5–0.99 ng/mL, 75 % at 1–1.99 ng/mL and 95 % at ≥ 2 ng/mL [23], and increased sensitivity has been reported in patients with shorter PSA doubling times and higher grade group disease[24]. Subsequent studies have demonstrated that overall treatment strategies or RT

Table 3
Pre-treatment investigations.

What investigations should be sought for patients with a rising or persistently elevated PSA following radical prostatectomy?	Level of evidence(91)	References
3.1. Conventional imaging with computed tomography and whole-body bone scan has low sensitivity at PSA < 10 ng/mL and should not routinely be performed in asymptomatic patients.	2	[6,21,22]
3.2. PSMA PET is a more sensitive modality for detecting recurrence post-prostatectomy, especially nodal and distant disease. When a decision has been made to proceed with salvage radiation therapy, and particularly if the PSA is ≥ 0.2 ng/mL, a PSMA-PET prior to commencing treatment is recommended.	2	[17,23,31,93–95]
3.3. A negative PSMA PET does not exclude local recurrence and patients should still be offered salvage radiation therapy in this context if clinically appropriate.	2	[31–34]
3.4. Where positive findings on PSMA PET may alter management (e.g detection of oligometastatic disease) consider confirmation with correlative imaging or biopsy.	5	
3.5. MRI can be a valuable modality for detecting or providing better anatomical delineation of local recurrence.	2	[6,21,36,37]

planning approaches are altered based on PSMA-PET results in 34–87 % of patients, demonstrating the utility of this modality[25–27].

While PSMA-PET is more sensitive than other imaging modalities, it is still limited by the spatial resolution of PET and so may not detect small deposits of disease < 4 mm[28]. Furthermore, 5–10 % of prostate cancers do not express PSMA which may result in a false negative result, while false positives can occur with benign inflammatory lesions, sacral/coeliac ganglia, bone fractures, Paget's disease deposits and other malignancies[29,30]. PSMA-PET also has relatively poor sensitivity for local recurrence in the prostate bed, especially at low PSA levels, due in part to the urinary excretion of PSMA and the potential of urinary incontinence causing high tracer activity in the proximal urethra. A negative PSMA-PET should therefore be used as a tool to exclude metastatic disease rather than detect local recurrence, and patients with a negative PSMA-PET should be offered SRT if clinically appropriate (Table 3)[31,32]. In fact, there is prospective evidence to suggest that a negative pre-salvage PSMA-PET predicts a higher likelihood of response to SRT when compared to a positive scan[33,34]. One option for improving the sensitivity of PSMA-PET in the surgical bed is to administer furosemide, an approach which is now recommended in European guidelines (20 mg i.v, shortly before or after the administration of ^{68}Ga-PSMA)[35].

Multiparametric MRI (mpMRI) can also be of value in detecting local recurrence, demonstrating increasing sensitivity as PSA levels rise. Detection rates for local recurrence were similar between PSMA-PET and mpMRI in a small, prospective, international trial conducted by Emmett et al.,[36] while a biopsy validated study by Lindenbergh et al, reported that mpMRI showed increased sensitivity (83 % vs. 57 %) but reduced specificity (52 % vs. 86 %) when compared to PSMA-PET for detecting recurrences within the prostate bed[37]. mpMRI can also be a valuable correlative imaging modality for equivocal PET findings as well as providing better anatomical delineation of macroscopic recurrent disease when planning RT[6,38,39].

Recommended dose and fractionation

While previous retrospective series and *meta*-analyses of SRT have suggested improved biochemical control rates with increasing doses of

Table 4
Recommended dose and fractionation for post-prostatectomy radiation therapy.

What is the recommended dose and fractionation for post-prostatectomy radiation therapy?	Level of evidence(91)	References
4.1. A dose of 64–66 Gy (EQD2) to the prostate bed is recommended in the salvage setting	1	[40,41]
4.2. In patients with macroscopic prostate bed recurrence, the electively treated prostate bed should be treated to a dose of 64–66 Gy (EQD2), while gross recurrence on imaging may be treated to doses ≥ 70–74 Gy (EQD2), respecting normal tissue constraints.	5	
4.3. Moderate hypofractionation (e.g. 52.5 Gy/20 fractions to the electively treated prostate bed) can be considered as an alternative fractionation schedule	2	[2,45,51]
4.4. Stereotactic body radiation therapy (SBRT) to the prostate bed is currently investigational and should not be administered outside of a clinical trial setting.	5	
4.5. A dose of 64 Gy in 32 fractions to the prostate bed is recommended in the adjuvant setting.	1	[1,2,6]

RT, two recent prospective randomised trials have not demonstrated a benefit of dose escalation[6,13,14,40,41]. The SAKK 09/10 trial randomly assigned 350 patients to conventional dose (64 Gy) or dose intensified (70 Gy) SRT to the prostate bed without hormonal therapy. With a median follow up of 6.2 years there was no significant difference in median FFBF (8.2 years versus 7.6 years, HR 1.14, 95 % CI 0.82–1.60) or estimated 6 year FFBF (62 % versus 61 %) in the 64 Gy and 70 Gy arms respectively[40]. There was also no significant difference in clinical PFS, time to hormonal therapy or overall survival. Patients treated to 70 Gy experienced higher rates of late grade 2 gastrointestinal toxicity (20 % versus 7.3 %, OR for grade ≥ 2 GI toxicity 2.20, 95 % CI 1.21–4.00; p = 0.009) as well as a more pronounced and clinically relevant worsening in acute urinary symptoms, while other acute and late toxicities as well as patient reported outcomes were not significantly different. Median PSA at randomisation was 0.3 ng/mL, and 75 % of patients had a PSA of ≤ 0.5 ng/mL.

These results are supported by a smaller, single centre, prospective randomised controlled trial by Qi et al., which enrolled 144 patients with either pT3-4 disease, positive surgical margins or PSA ≥ 0.2 ng/mL receiving PPRT (33 % adjuvant RT, 67 % salvage RT) to a dose of 66 or 72 Gy[41]. A high proportion of patients received whole pelvis RT in addition to prostate bed RT (87.5 %) and hormonal therapy was not allowed. Over a median follow up period of 48.5 months there was no difference in 4 year biochemical PFS (bPFS) between the groups (75.9 % versus 82.6 %; P = 0.299). On subgroup analysis, patients with Gleason score 8–10 did have significantly improved 4 year bPFS when treated to 72 Gy (55.7 % in the 66 Gy cohort versus 79.7 % in the 72 Gy cohort, P = 0.049). There was no difference detected in MFS or OS between the groups, however the event rate was low, with only 10 patients developing distant metastatic disease and 6 deaths. There were also no differences in grade ≥ 2 acute or late gastrointestinal or genitourinary toxicity between the groups and rates of toxicity were overall low, with all patients being treated with IMRT/VMAT technique using daily cone beam CT (CBCT) for image guidance. The marginal benefit of dose escalation in the subset of patients with Gleason 8–10 disease (P = 0.049) was based on data from only 55 patients and may have been confounded by use of WPRT, which was not stratified for, as well as a uniform lack of hormonal therapy across the trial. Therefore, there is currently insufficient evidence to support dose escalation and we recommend that a dose of 64–66 Gy (EQD2) be delivered to the prostate bed in the salvage setting (Table 4). In cases of macroscopic prostate bed recurrence, higher doses of RT ≥ 70–74 Gy EQD2 to gross disease should be considered if normal tissue dose constraints allow. This recommendation is supported by a recent multicentre retrospective trial demonstrating a potential benefit in PFS (5 year PFS 73 % vs 60 %; p = 0.03) as

well as acceptable mid-term safety profile (median follow up 54 months, Grade ≥ 2 GU toxicity 12 %), when delivering doses ≥ 72 Gy to patients with macroscopic local recurrence detected on functional imaging using either mpMRI or PET[42].

Evidence in support of moderate hypofractionation post-prostatectomy is not as established as in the definitive setting[43,44], however there is a considerable amount of international experience with this approach. Whilst there are no prospective randomised phase III trials comparing conventional and moderately fractionated PPRT, available data, which is primarily retrospective, suggests comparable rates of biochemical control and toxicity[45–48]. Moreover, both RADICALS-RT and RADICALS-HD allowed patients to be treated to a dose of either 66 Gy in 33 fractions or 52.5 Gy in 20 fractions and a recent exploratory toxicity analysis of RADICALS-RT demonstrated similar toxicity profiles between the two schedules with the only significant difference being higher rates of grade 1 to 2 cystitis in the first two years after treatment for the conventionally fractionated cohort as compared to the hypofractionated cohort (30 % versus 20 %; P = 0.02) [2,49,50]. We have therefore concluded that moderate hypofractionation is a reasonable and standard option for SRT.

Recently, the NRG-GU003 trial, which compared 66.6 Gy in 37 fractions with 62.5 Gy in 25 fractions (equivalent dose in 2 Gy fractions (EQD2) 70.3 Gy using an α/β ratio of 2 Gy), reported non-inferiority of hypofractionated RT in terms of 2 year patient reported GI and GU toxicity, however longer term follow up is needed to properly assess disease outcomes and late toxicity results with this dose[51].

When treating in the adjuvant setting, a dose of 64 Gy in 32 fractions is recommended, in line with previous guidelines and based on contemporary trials of adjuvant versus salvage RT[1–3,6].

Role for SBRT

There is very limited evidence on the use of ultra hypofractionated stereotactic body radiation therapy (SBRT) to treat the prostate bed following prostatectomy, with no randomised trials having yet reported results. The single arm, phase II, SCIMITAR II trial recently reported early quality of life and toxicity results (median follow up 29.5 months) for 100 patients treated to a dose of 30–34 Gy in 5 fractions to the prostate bed, with either CT- or MRI guided RT, and reported low levels of acute and late toxicity, but has not reported on biochemical outcomes [52]. Otherwise, evidence for SBRT is limited to small phase I and II trials as well as observational studies[53–55]. At this stage we do not recommend that SBRT to the prostate bed be delivered outside of a clinical trial setting and await longer term efficacy and toxicity results from randomised studies.

Role for androgen deprivation therapy

There are now four published randomised trials as well as an upcoming *meta*-analysis which have sought to assess the benefit of adding ADT to SRT[49,56–60]. The first trial, RTOG 9601, randomised 760 patients to salvage RT with or without 24 months of bicalutamide. PSA at randomisation was relatively high, ranging from 0.2 − 4.0 ng/mL with a median of 0.6 ng/mL. At 12 years follow up, overall survival was significantly improved with the addition of bicalutamide (76.3 % versus 71.3 %, HR 0.77) along with improved rates of biochemical progression and distant metastases. Subgroup analyses demonstrated that this survival benefit was seen in patients with pretreatment PSA > 0.7 ng/mL, Gleason score ≥ 7 and positive surgical margins[56]. A secondary analysis found that patients with a pretreatment PSA ≤ 0.6 ng/mL had a significantly increased risk of other-cause mortality when treated with two years of bicalutamide, with an estimated increased risk of death of 9.4 % at 12 years (95 % CI 2.2 % − 16.7 %), increased rates of grade 3–5 cardiac and neurologic toxicity and no benefit in overall survival or rate of distant metastases[61].

The second trial, GETUG-AFU 16, randomised 743 patients to SRT to the prostate bed +/- pelvic nodes with or without 6 months of goserelin [57]. The median pretreatment PSA was 0.3 ng/mL, although patients with PSA up to 2.0 ng/mL were enrolled. The addition of goserelin significantly improved 10 year metastasis free survival (MFS) from 69 % to 75 %, however it should be noted that no routine surveillance scans were required to assess for metastatic disease. Importantly, MFS is currently the only validated surrogate endpoint for overall survival in localised prostate cancer, while the use of biochemical endpoints in trials of ADT may be confounded by the effect of ADT in delaying testosterone recovery[62]. There was no improvement in overall survival and there were no differences on post-hoc analysis between histopathological subgroups (Gleason score, surgical margin status, seminal vesicle involvement, PSA doubling time), although longer follow up is needed to achieve sufficient power to accurately assess these endpoints.

The third trial, RTOG 0534 SPPORT, utilised a three arm trial design and randomly assigned 1972 patients to either prostate bed RT (PBRT) alone, PBRT plus short term ADT (4–6 months total, beginning 2 months prior to RT) or PBRT plus short term ADT and pelvic lymph node RT (PLNRT)[58]. Median baseline PSA was 0.35 ng/mL and the prescribed RT dose was 64.8 – 70.2 Gy in 1.8 Gy fractions to the prostate bed and 45 Gy in 1.8 Gy fractions to the pelvic lymph nodes. Final analysis demonstrated 5 year freedom from progression rates of 70.9 % in the PBRT alone group, 81.3 % in the PBRT plus ADT group and 87.4 % in the PBRT plus ADT and PLNRT group, with the differences between all cohorts reaching statistical significance (p < 0.01). Further post hoc analysis demonstrated significantly reduced use of second salvage ADT with the addition of short term ADT to PBRT (adjusted HR 0.58, p < 0.0001). However there were no significant differences seen in MFS or OS between any of the groups, acknowledging the relatively short median follow up of 8.2 years. Given the pre-existing evidence suggesting a reduced benefit of ADT in patients with lower pre-salvage PSA, an unplanned post-hoc analysis was performed according to baseline PSA (the median PSA of 0.35 ng/mL was used as the cutoff). The benefit in PFS from adding ADT to PBRT was similar for the PSA groups of ≤ 0.35 ng/mL or > 0.35 ng/mL as well as across other histopathological subgroups.

The fourth trial, RADICALS-HD, was the first to compare different durations of ADT combined with postoperative RT. 2,839 patients were randomised to PPRT (35 % of patients were treated with ART) plus either no ADT, 6 months ADT or 24 months ADT[49,59]. While three-way randomisation was encouraged, patients could be enrolled in a two-way randomisation between either no– versus short term ADT or short versus long term ADT. As may be expected, more favourable risk patients were enrolled in the 0 versus 6 month randomisation as compared to the 6 versus 24 months randomisation, with lower rates of Gleason 8–10 disease (11 % versus 29 %), pathological T3b/4 (16 % versus 30 %) and fewer patients with multiple risk factors (15.5 % versus 34.6 %). Median pretreatment PSA was 0.22 ng/mL and the primary endpoint was MFS. Over a median follow up period of 9 years, 6 months of ADT did not improve MFS or OS when compared to no ADT, but did improve freedom from second salvage ADT (HR 0.54; CI: 0.42–0.70; 73 % vs 82 % at 10 years). In the short versus long comparison, long term ADT significantly improved MFS (HR 0.77; CI: 0.61–0.97; 72 % vs 78 % at 10 years) as well as freedom from second salvage RT (HR 0.73; CI 0.59–0.91; 68 % vs 75 % at 10 years), with no improvement in OS. This finding was consistent across all prespecified subgroups, including baseline PSA and degree of co-morbidity, and there was no evidence of differential effects in any of the exploratory subgroup analyses. It should be noted however, that the median PSA in RADICALS-HD was significantly lower than in RTOG 9601 and that too few patients had pre-radiotherapy PSA of greater than 0·7 to test for the overall survival effect reported in the earlier study.

Finally, the upcoming DADSPORT *meta*-analysis is pooling results from all four of the abovementioned trials. Preliminary results, presented in abstract form, demonstrate no clear evidence of an OS benefit with the addition of ADT, but do show a small but significant absolute

Table 5
Role of androgen deprivation therapy with post-prostatectomy radiation therapy.

What is the role of hormonal therapy in conjunction with post-prostatectomy radiation therapy?	Level of evidence(91)	References
5.1. In select patients, the addition of androgen deprivation therapy (ADT) to salvage radiation therapy improves biochemical control and distant metastasis-free survival.	1	[49,56–59]
5.1.1. An overall survival benefit of hormonal therapy may be limited to patients with pre-salvage PSA levels > 0.6 ng/mL.	3	[61]
5.2. Patients should be risk stratified. Those likely to gain the most absolute benefit from the addition of ADT are those at highest risk of poor outcomes with salvage radiation therapy alone (e.g. pre-salvage PSA > 0.6 ng/mL, ISUP grade group 4 or 5, pT3b/T4, short PSA doubling time).	5	[17,18,49,56–59]
5.3. The potential oncological benefit of androgen deprivation should be weighed against possible toxicities including metabolic dysregulation, reduction in bone mineral density, cardiovascular and cognitive effects, taking into account patient age and comorbidity.	5	[56]
5.4. The optimal duration of concurrent ADT is unknown. 6–24 months of treatment is recommended, with the longer duration of treatment recommended in patients with multiple high-risk features	5	[17,49,56–59]
5.5. Patients receiving elective nodal irradiation should be considered for concurrent ADT.	5	

improvement in MFS with the addition of short term ADT as compared to no ADT (HR 0.82, 95 % CI 0.70–0.96)[60]. We await the formal publication of DADSPORT which may provide further valuable information on the possible benefits of ADT, particularly between subgroups, in the postoperative setting.

Based on the significant body of accumulated prospective evidence, the following conclusions can be made (Table 5). Those with lower risk disease appear to do well with RT alone, however the addition of short term ADT may result in a small improvement in MFS in some patients and delay time to second salvage ADT, a treatment which is commonly lifelong. Meanwhile there are patients with higher risk disease who will derive additional MFS benefit from further intensification of treatment with long course ADT. Unfortunately, it remains unclear how best to define these groups to determine who should receive ADT and for how long. While more accurate and nuanced tools are awaited, we recommend that each patient be risk stratified based on standard clinico-pathological features. Established risk factors for distant metastases and prostate cancer mortality include high pathological ISUP grade group (ISUP grade group ≥ 4), shorter PSA doubling time (<12 months), higher pre-salvage PSA (>0.6 ng/mL) and high pathological T stage (≥pT3b)[18,63]. Those patients at highest risk of poor outcomes with RT alone are likely to gain the most absolute benefit from the addition of ADT, and those with multiple high risk features are likely to derive additional benefit from a longer course of treatment. As with all interventions, the potential benefit of ADT should be weighed against possible toxicities including metabolic dysregulation, reduction in bone mineral density, cardiovascular and cognitive effects, while taking into account patient age, life expectancy and preferences.

Role for elective nodal coverage

The RTOG 0534 SPPORT trial is the only randomised controlled trial to assess the role of elective PLNRT following biochemical recurrence post-prostatectomy[58]. This trial is summarised in the previous section on the role for ADT. Briefly, the addition of PLNRT resulted in improved 5 year freedom from progression when compared to PBRT plus ADT as well as to PBRT alone (87.4 % versus 81.3 % versus 70.9 % respectively) as well as improved time to second salvage ADT (Adjusted HR 0.58, p 0.0002). The analysis of patients stratified by baseline PSA indicated that the freedom from progression benefit of PLNRT appeared greatest in patients with PSA above 0.35 ng/mL, although this comparison did not reach statistical significance and the trial was not powered to assess these subgroups independently. Toxicity results demonstrate that treatment was generally well tolerated with low absolute toxicity rates, however the addition of PLNRT did result in significantly increased rates of acute grade 2 + gastrointestinal toxicity (4 % versus 7 %) as well as grade 2 + acute (2 % versus 5 %) and late (2 % versus 4 %) haematological toxicity and grade 3 + acute haematological toxicity (<1% versus 3 %). A *meta*-analysis, published before toxicity data was available for RTOG 0534, found that PLNRT increased the risk of acute gastrointestinal toxicity (RR 1.76, p < 0.001), with no significant differences in acute or late genitourinary toxicity[64]. While not routinely reported in contemporary prostate cancer trials, there is evidence to suggest that rates of lower limb and genital lymphoedema are increased with PLNRT, especially following pelvic lymph node dissection, and evidence from other anatomical subsites within the pelvis demonstrates a long term risk of pelvic insufficiency fracture following nodal irradiation[65,66].

Some limitations of RTOG 0534 include the lack of molecular imaging techniques such as PSMA-PET for pre-treatment staging as well as

Table 6
Role of elective nodal coverage.

What is the role of pelvic lymph node irradiation?	Level of evidence(91)	References
6.1. Elective pelvic lymph node radiation therapy improves rates of biochemical control and time to second salvage ADT when added to salvage prostate bed radiation therapy and androgen deprivation therapy, and can be considered. Improved metastasis-free survival and overall survival has not been demonstrated to date.	1	[58,96]
6.2. Elective pelvic lymph node radiation therapy may be discussed as an option with patients who have had minimal or no lymph node dissection and/or are at high risk of microscopic nodal involvement (e.g., ISUP grade group 4 or 5, pT3/4, pre-operative PSA > 20 ng/mL, persistently elevated PSA with clear margins, pre-salvage PSA > 0.35 ng/mL).	5	[6,58,70,96]
6.3. Patients with pathologically involved lymph nodes at prostatectomy, who are being considered for salvage treatment, should receive pelvic lymph node radiation therapy in addition to prostate bed radiation therapy.	2	[92]
6.4. A dose of 45–50 Gy (EQD2) to the elective pelvic lymph nodes is recommended.	5	[6,58,71]
6.5. Involved nodes on imaging (e.g., detected with PSMA PET) should be treated to a higher dose, aiming for doses between 60–74 Gy (EQD2), while respecting normal tissue dose constraints and using appropriate image guidance.	5	[92,97]
6.6 Pelvic lymph node radiation therapy increases rates of gastrointestinal and haematological toxicity, as well as the risk of lymphoedema and pelvic insufficiency fractures. However, reported rates of severe toxicity are low.	1	[41,58,64–66,98,99]

Table 7
Post-prostatectomy radiation therapy planning.

How should patients be simulated and how should treatment volumes be delineated?	Level of evidence(91)	References
7.1 Simulation	5	
Patients should evacuate their bowels and a bladder filling protocol should be used to achieve a comfortably full bladder at the time of planning and during treatment.		
7.2. Target volume delineation of gross macroscopic recurrence	5	
PSMA PET fusion may be used to aid in identifying sites of macroscopic local recurrence or involved nodal disease.		
MRI fusion may be used to help identify the vesicourethral anastomosis (VUA) and penile bulb, as well as to better delineate sites of PSMA-avid local recurrence.		
Any macroscopic disease as determined clinically and on imaging should be contoured as GTV.		
7.3. Clinical target volume delineation of the prostate bed	4	
Inferior border: The inferior border of the CTV should be 5–10 mm below the VUA with the larger margin being more appropriate if not using MRI or IV contrast to assist in delineating the anastomosis. The inferior border should also be extended lower to include all surgical clips inferiorly.		
The anastomosis is best identified on axial, coronal and sagittal reconstructions on T2 weighted MRI. On CT it can be identified as the first slice below where urine is last visible. When the anastomosis is not clearly defined, the inferior border will be the slice above the penile bulb.		
Anterior border: From the lower border of the CTV to 2–3 cm superior, the anterior border of the CTV is the posterior aspect of the symphysis pubis, incorporating at least 1.5 cm (craniocaudally) of the bladder neck. More superiorly, the anterior border of the CTV wraps around the lateral aspects of the posterior bladder wall to extend 1.5 cm anteriorly.		
Posterior border: The posterolateral rectal recesses (i.e. the space delineated by the levator ani and the anterior rectal wall) are at risk for recurrence and should be encompassed in the middle portion of the CTV. Ensure a minimum 5 mm coverage on both sides of the rectum, aiming to cover any residual seminal vesicles or surgical clips.		
The risk of posterolateral recurrence inferior to the anorectal junction is low, therefore at this level the CTV does not need to wrap around posteriorly.		
More superiorly, the posterior border of the CTV is the anterior mesorectal fascia.		
Lateral border: The medial border of the levator ani muscle or obturator internus muscle.		
Superior border: The superior border should encompass the seminal vesicle bed as defined by non-vascular clips, up to the level of the cut end of the vas deferens. In situations where the seminal vesicles were not pathologically involved by tumour, and there is no involvement of the prostatic base, the superior border should not extend more than 4.5 cm above the VUA.		
If the seminal vesicles were pathologically involved, ensure any residual seminal vesicles are included in CTV.		
7.4. Target volume delineation for pelvic nodal irradiation	5	
Target volume delineation for pelvic nodal irradiation should be according to NRG Oncology guidelines.		[97]
7.5. Planning target volume delineation	4	[87,100]
The CTV to PTV expansion should be dependent on the image guidance technique used and the experience of the treating department.		
Daily CBCT imaging is recommended, ideally matched to soft tissue.		
Anisotropic expansions can be considered to account for differences in degree of movement between the upper and lower prostate bed.		
The upper and lower portions of the prostate bed can be divided at the level where the CTV moves away from the pubic symphysis.		
As a guide, when using daily soft tissue imaging, the CTV should be expanded by 5–7 mm in the lower prostate bed to generate the PTV. In the upper prostate bed, margins should be 5–10 mm, with the more generous margin in the anterior/posterior direction where movement is greatest.		
The nodal CTV should be expanded by 5–7 mm to generate the nodal PTV.		

the significant proportion of patients, around one-third, who did not undergo pelvic lymph node dissection. In the two thirds of patients who did undergo lymph node dissection, the median number of nodes examined was six. Taken together, this raises some uncertainty around the potential benefit of PLNRT in patients who have received more extensive nodal dissections or those who have been staged with modern imaging techniques[67,68]. It remains unclear which subgroups of patients will benefit from the addition of PLNRT (Table 6). However, it is an option which should be discussed with patients who have had minimal or no lymph node dissection, especially those at high risk of microscopic nodal involvement based on clinicopathological parameters (eg. ISUP grade group 4 or 5, pT3/4, pre-operative PSA > 20, persistently elevated PSA with clear margins, pre-salvage PSA > 0.35 ng/mL) [58,69,70]. The benefit of nodal irradiation in the absence of concurrent ADT is unknown and therefore patients being considered for nodal RT should also be considered for concurrent ADT.

When prescribing PLNRT, doses in line with contemporary randomised trials should be utilised, ranging from 45-50 Gy (EQD2) [41,58,71]. For those patients who present with lymph node involvement detected on imaging (e.g. PSMA-PET) and who are being considered for salvage treatment, we recommend a higher dose be delivered to sites of macroscopic nodal disease. While the optimal dose is unknown, we recommend aiming for doses between 60–74 Gy (EQD2) depending on lymph node bulk and adjacent normal structures while using appropriate image guidance.

Clinical target volume delineation

The increasing use of PSMA-PET following biochemical recurrence has allowed for a more detailed and systematic assessment of the anatomic location of recurrent disease than was previously available. Recent studies have used PSMA-PET to describe the distribution of local recurrences after prostatectomy and therefore identify areas within current consensus CTV guidelines where coverage could be adjusted. Particularly relevant is the recent work by Horsley et al., which assessed 1049 PSMA-PET scans, identified 140 sites of local recurrence, and then assessed whether these recurrences occurred inside or outside the FROGG and RTOG consensus CTVs[72]. A similar study by Sonni et al., included 226 patients with PET positive recurrent disease, of which 127 patients had recurrence confined to the prostate bed, and assessed the location of these recurrences in relation to the RTOG CTV definition [73]. Following independent, critical review of contemporary patterns of failure literature, the working group developed a set of adjustments to the previous consensus CTV (Table 7). These adjustments were presented in an open forum at the FROGG workshop, discussed among attendees and then circulated to the FROGG committee and expert panel for review, comment and discussion over several meetings, after which the following consensus adjustments to the CTV were recommended. Representative, annotated, axial and sagittal CT images from a sample patient are depicted in Fig. 1. A table highlighting the changes made between the original 2008 FROGG guidelines and the current guidelines is also provided in.(See Table 9).

- Inferior border: The area around the vesicourethral anastomosis (VUA) is the commonest site of local recurrence post prostatectomy [72–74]. Both studies by Horsley et al., and Sonni et al., identified a proportion of recurrences which occurred below the inferior borders of contemporary CTV guidelines. In relation to the FROGG guidelines, up to 9 % of recurrences were identified > 5 mm below the VUA, which would place them below the previously recommended inferior CTV border[72]. Despite this, the reported rates of local failure following PPRT remains extremely low. A recent series of 409 patients treated in accordance with FROGG guidelines, of whom 119 experienced biochemical failure, identified only 2 local failures (0.5 % of patients treated) within the prostate bed[75]. This may be explained by the generous CTV to PTV margin that had previously been recommended. As image guidance capabilities improve and PTV margins reduce, it is important to ensure that the CTV accurately encompasses the area at risk. An important caveat to the above is in how the VUA is identified. Previous FROGG guidelines have used the first slice below where urine is last visible as a CT surrogate for this anatomic landmark. However, a study by Lim Joon et al., which co-registered simulation CT and T2 weighted MRI images for patients being planned for post-prostatectomy RT, found that the MRI defined VUA was inferior to the CT defined VUA in a majority of cases (88 %), with a median observed difference of 5 mm[76]. Therefore,

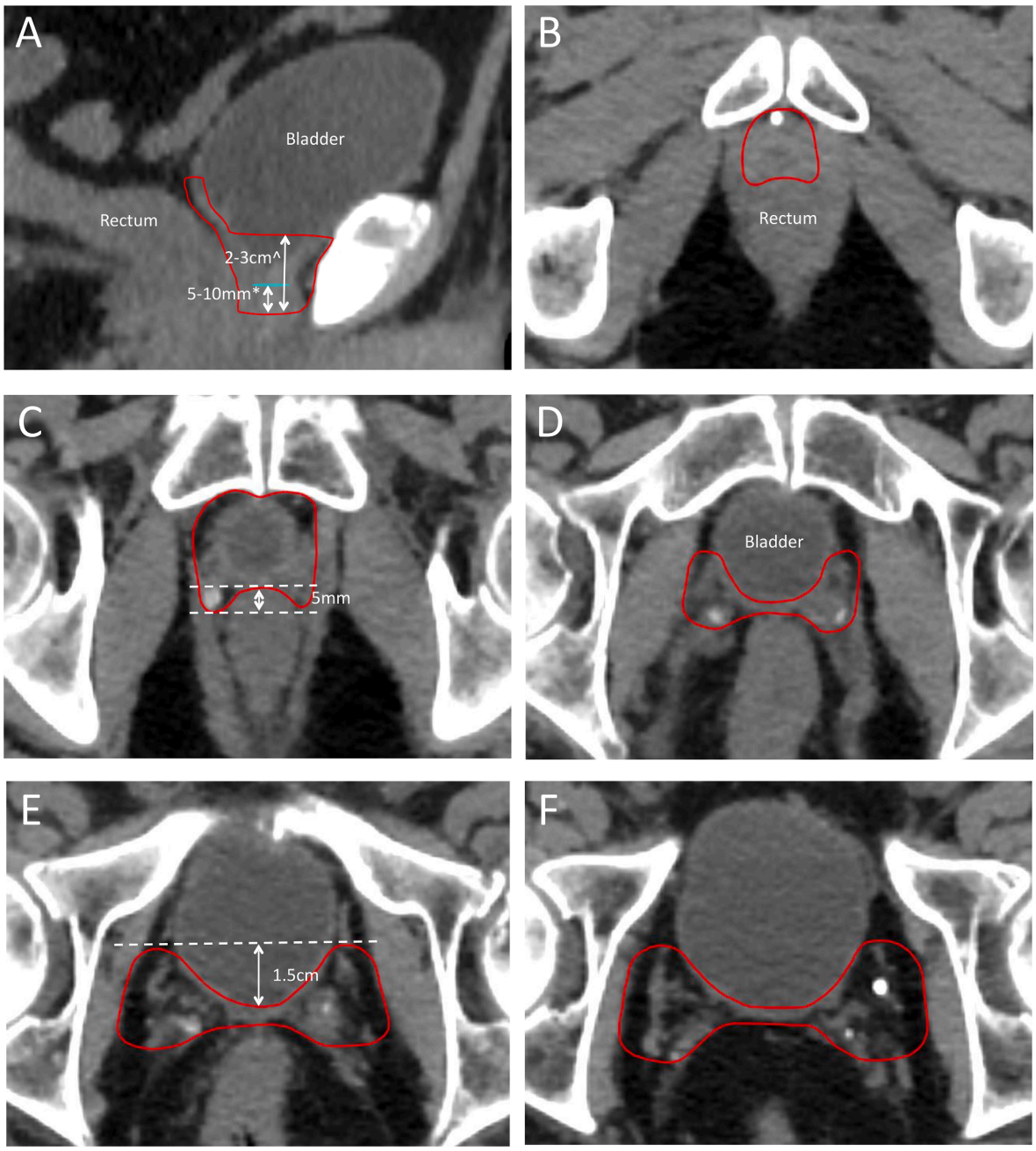

Fig. 1. Serial CT slices of a sample post-prostatectomy patient demonstrating the contouring guidelines. CTV, red; vesicourethral anastomosis (VUA), cyan. (A)* The inferior border is 5–10 mm below the VUA depending on how the VUA has been delineated, in this example the inferior border is 10 mm below the VUA. (A)^The lower anterior border lies 2–3 cm above the inferior border of the CTV, incorporating at least 1.5 cm of the bladder neck. (C) The posterolateral rectal recesses should be covered to a depth of 4–5 mm on both sides of the rectum. (E) The upper anterior border wraps around the lateral aspect of the posterior bladder wall to extend 1.5 cm anteriorly. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

when using CT alone for planning, consideration should be given to extending the inferior border to 10 mm below the VUA. If MRI is being used, a margin of 5 mm below the VUA can continue to be used.

- Posterior border: The posterolateral rectal recesses are at significant risk of local recurrence, with the Horsley study demonstrating 26 % of recurrences occur at this site[72]. Coverage of this region needs to be balanced against the increasing rates of gastrointestinal toxicity that would be expected with increasing coverage of the rectal wall. We recommend that this region be covered to a depth of 5 mm on both sides of the anterior rectal wall. This recommendation only applies to the middle portion of the CTV. More inferiorly (at or below the anorectal junction) there is no need to extend the CTV posteriorly around the anterior rectal wall as this area does not appear to be at significant risk of recurrence. Superiorly, the posterior border of the CTV is defined by the anterior mesorectal fascia.
- Anterior border: Previous guidelines recommend the anterior CTV border extend superiorly up a significant portion of the posterior aspect of the pubic symphysis, resulting in a large volume of normal bladder being irradiated and significant rates of urinary toxicity (>50 % acute grade 2 in both RAVES and RTOG 0534)[1,58]. Contemporary patterns of failure data demonstrate that the risk of anterior recurrences above the bladder neck and behind the pubic symphysis is low. While we acknowledge the limitations of PSMA-

PET in detecting recurrent disease at this location due to the presence of tracer within the bladder, studies which have incorporated multiparametric MRI (mpMRI) or hybrid PET/MRI to detect local recurrence also appear to show that this site is at low risk[77–81]. Furthermore, expert consensus and experience is that recurrences are rarely if ever seen at this location. It is therefore reasonable to lower this antero-superior border to 2–3 cm superior to the inferior CTV border, ensuring at least 1.5 cm of bladder neck is covered.

- Superior Border: Previous histopathological studies have shown that the risk of involvement of the distal portion of the seminal vesicles (SVs) is extremely low, even in cases where the SVs are pathologically involved[82,83]. Horsley et al., found that 6 % of recurrences occurred > 45 mm superior to the VUA, with pathological involvement of the base of the prostate being a significant predictor of recurrence at this level[72]. Recent Francophone Group of Urological Radiotherapy (GFRU) guidelines have recommended reducing the superior extent of the CTV in cases where the SVs are not involved to 1 cm above the pubic symphysis[84]. Our preference is to avoid using a bony surrogate as the position of VUA can be variable in relation to the pubic symphysis. Therefore, in cases where there is no pathological seminal vesicle involvement and no involvement of the prostatic base, it is reasonable for the superior border to include up to the cut end of the vas deferens and it should not extend more than 4.5 cm above the VUA.

Comparison to recently published guidelines

A number of other modern consensus guidelines exist for delineation of the prostate bed CTV, namely those of GFRU[84], ESTRO-ACROP[85] and PERYTON[86]. Like our own, these guidelines have sought to refine previous guidelines by incorporating modern imaging modalities, patterns of failure data, image guidance and radiotherapy techniques, with the aim of improving prostate cancer outcomes and reducing treatment related toxicity. Our guidelines were independently developed but share many similar recommendations with these publications, and there is strength in the fact that separate international research groups have come to similar conclusions. Furthermore, having different sets of guidelines is valuable as it can highlight areas of international agreement, differences in approach based on patterns of expert practice, as well as points of ongoing uncertainty which may then guide the development of future research.

Similarities between the guidelines include extending the inferior border to ensure adequate coverage of the VUA, reduction of the height of the anterior border where it runs along the posterior edge of the pubic symphysis to reduce unnecessary coverage of normal bladder, an emphasis on the importance of coverage of the posterolateral rectal recesses and reduction of the superior border in cases where there is no seminal vesicle involvement.

One key difference in our approach is in our preference to avoid using bony surrogates when defining the CTV. In our experience, the position of the VUA (and therefore, the relative location of potential recurrence) can be variable in relation to bony landmarks and therefore our guidelines primarily use the VUA as a spatial reference point.

A table comparing similarities and differences between the recently published guidelines has been included in Table 10.

Planning target volume delineation

Contemporary RT techniques, planning software and image guidance allows for the possibility of tighter planning target volumes (PTV) margins. A guide has been provided on how this may be approached (Table 7). A recent study by Bell et al., assessed six different PTV expansions and three different tissue matching techniques including matching to both bony anatomy and soft tissue. Unsurprisingly, daily matching to soft tissue allowed for reduced PTV margins with lower rates of geographic miss. Ultimately however, the CTV to PTV expansion

Table 8
Organs at risk dose constraints.

Ideal dose constraints listed below are an example of what may be achievable using modern radiation therapy techniques. Target coverage should not be compromised in order to meet the ideal constraints.	Level of evidence[91] 1–3	References [2,43,88–90,97]
8.1 Dose and volume objectives: daily fractions of 2 Gy		
Rectum:		[88]
Acceptable		
V50 Gy < 50 %		
V60 Gy < 35 %		
V65 Gy < 25 %		
V70 Gy < 20 %*		
Ideal		
V40 Gy < 51 %		
V60 Gy < 25 %		
Bladder:		[43]
Data regarding dose-volume toxicity relationships remain poorly defined in the post-prostatectomy setting, however the following can be used as a guide.		
Acceptable		
V50 Gy < 80 %		
V65 Gy < 50 %		
V70 Gy < 35 %*		
Ideal		
V50 Gy < 50 %		
V60 Gy < 25 %		
V70 Gy < 5 %*		
*Care should be taken to minimise dose greater than prescription within rectum and bladder as well as to avoid dosimetric hotspots in the vicinity of the vesicourethral anastomosis.		
Small bowel:		
Avoid dosimetric hotspots in loops of small bowel.		
As a guide, aim D1cc < 50 Gy.		
In the case of pelvic nodal coverage, the peritoneal cavity should be contoured, aiming for V45 Gy < 195 cc, however PTV coverage should take priority over a specific dose-volume constraint.		
Femoral heads:		[88]
Acceptable		
V50 Gy < 5 %		
Ideal		
V35 Gy < 15 %		
V45 Gy < 1.5 %		
8.2 Dose and Volume Objectives: 52.5 Gy in 20 fractions		
Rectum:		
Acceptable		
V40 Gy < 50 %		
V48 Gy < 35 %		
V52 Gy < 25 %		
V56 Gy < 20 %		
Bladder:		[43]
Data regarding dose-volume toxicity relationships remain poorly defined in the post-prostatectomy setting, however the following can be used as a guide.		
Acceptable		
V40 Gy < 80 %		
V48 Gy < 50 %		
Ideal		
V40 Gy < 50 %		
V48 Gy < 25 %		
Care should be taken to minimise doses greater than prescription within rectum and bladder as well as to avoid dosimetric hotspots in the vicinity of the vesicourethral anastomosis.		
Small bowel:		
Avoid dosimetric hotspots within loops of small bowel.		
As a guide, aim D1 cc < 46 Gy.		
Femoral heads:		
V43 Gy < 5 %		

Table 9
Comparison of clinical target volume definitions between the 2008 and 2024 FROGG Guidelines.

	2008 FROGG Guidelines(5)	2024 FROGG Guidelines
Inferior Border	5–6 mm below the VUA, but should extend lower to include all surgical clips inferiorly.	5–10 mm below the VUA, with the larger margin being more appropriate if not using MRI or IV contrast to assist in delineating the anastomosis. Should extend lower to include surgical clips inferiorly.
Anterior Border	From the lower border of the CTV to 3 cm superior, the anterior border of the CTV is the posterior aspect of the pubic symphysis. More superiorly the anterior border of the CTV encompasses the posterior 1.5 cm of the bladder.	From the lower border of the CTV to 2–3 cm superior, the anterior border of the CTV is the posterior aspect of the symphysis pubis, incorporating at least 1.5 cm of the bladder neck. More superiorly, the anterior border of the CTV wraps around the lateral aspects of the posterior bladder wall to extend 1.5 cm anteriorly.
Posterior Border	The space delineated by the levator ani and anterior rectal wall should be encompassed within the CTV. Ensure a minimum 2 cm margin from the posterior extent of the CTV to the posterior rectal wall. More superiorly, the posterior border of the CTV is the anterior mesorectal fascia.	The posterolateral rectal recesses should be covered, aiming for a minimum 5 mm coverage on both sides of the rectum. At or below the level of the anorectal junction the CTV does not need to wrap around posteriorly. More superiorly, the posterior border of the CTV is the anterior mesorectal fascia.
Lateral Border	The medial border of the levator ani muscle or obturator internus muscle.	The medial border of the levator ani muscle or obturator internus muscle.
Superior Border	The superior border should encompass all of the seminal vesicle bed as defined by non-vascular clips and should include the distal portion of the vas deferens. If the seminal vesicles were pathologically involved by tumour, ensure any residual seminal vesicles are included in the CTV	The superior border should encompass the seminal vesicle bed as defined by non-vascular clips, up to the level of the cut end of the vas deferens. In situations where the seminal vesicles were not pathologically involved by tumour, and there is no involvement of the prostatic base, the superior border should not extend more than 4.5 cm above the VUA. If the seminal vesicles were pathologically involved, ensure any residual seminal vesicles are included in CTV.

should be dependent on the image guidance technique used and the experience of the treating department[87].

Dose constraints for organs at risk

Table 8 provides guidance on dose volume constraints when delivering PPRT with both conventionally fractionated and moderately hypofractionated treatment schedules. Acceptable and ideal constraints are listed for select structures. The listed ideal dose constraints are an example of what may be achievable using modern RT techniques and target coverage should not be compromised in order to meet these ideal constraints. The ideal constraints for conventionally fractionated RT to the rectum and femur are based on a secondary analysis of the RAVES trial data, which utilised an iterative knowledge based planning tool to re-plan 137 PPRT plans, resulting in more homogeneous PTV coverage and lower doses to specified OARs (rectum and left femur)[88]. These constraints were able to be achieved in 90 % of knowledge based plans. The remaining constraints have been collated from phase 3 trials with published toxicity data in both the post prostatectomy and intact settings as well as from the Quantitative Analysis of Normal Tissue Effects

Table 10
Comparison of prostate bed clinical target volume definitions between recently published guidelines.

	FROGG 2024	ESTRO ACROP(85)	GFRU(84)	PERYTON(86)
Inferior border	5–10 mm below the VUA. The larger margin being more appropriate if not using MRI or IV contrast to delineate the VUA. Should extend to include surgical clips inferiorly.	Use VUA as anatomic landmark and contour 8–12 mm below.	5 mm above the penile bulb.	≤2 mm above top of the penile bulb
Anterior border	From the lower border of the CTV to 2–3 cm superior, the anterior border is the posterior aspect of the symphysis pubis, incorporating at least 1.5 cm of the bladder neck. More superiorly, the anterior border wraps around the lateral aspects of the posterior bladder wall to extend 1.5 cm anteriorly.	Caudally, stop at the posterior margin of the pubic bone up to half to two thirds of the symphysis pubis Cranially, should cover 1–2 cm of the posterior bladder wall or stop at the posterior margin of bladder wall	Must fulfil 3 criteria: At least 1.5 cm of the bladder neck must be included. Must cover the posterior border of the pubic bone on at least 2/3 of its length. At least 3 cm are necessary between the lower and upper slices of delineation of the CTV along the pubic bone.	Inferior region: Along the pubic bone. Anterolateral angles on both sides should stop at the pubic bone. Superior region: First 0.5 cm of bladder wall. Anterolateral angles should stop at the height of 1/2 of the femoral heads.
Posterior border	The posterolateral rectal recesses should be covered, aiming for a minimum 5 mm coverage on both sides. At or below the level of the anorectal junction the CTV does not need to wrap around posteriorly. More superiorly, the border is the anterior mesorectal fascia.	Contour up to the anterior rectal wall. Include the antero-lateral angles of the rectum and existing surgical clips Cranially, up to the mesorectal fascia when visualized	The anterior border of the rectum, including the posterolateral angles on both sides of the rectum in 5 mm	Inferior region: The anterior rectal wall including posterolateral angles on both sides of the rectum in 5 mm Superior region: The anterior rectal wall including posterolateral angles on both sides of the rectum in 10 mm
Lateral border	The medial border of the levator ani muscle or obturator internus muscle.	The internal margins of the internal obturator muscles. More caudally, the internal margins of the internal obturator muscles or	Internal borders of the levator ani or obturator internus muscles.	Internal borders of the levator ani or obturator internus muscles.

(*continued on next page*)

Table 10 (*continued*)

	FROGG 2024	ESTRO ACROP(85)	GFRU(84)	PERYTON(86)
		the levator ani muscles		
Superior border	Encompass the SV bed as defined by non-vascular clips, up to the level of the cut end of the vas deferens. Where the SVs were not pathologically involved by tumour, and there is no involvement of the prostatic base, the border should not extend more than 4.5 cm above the VUA. If the SVs were pathologically involved, ensure any residual SVs are included.	Include region of both SVs with 3–5 mm "bridge". If no SV invasion, include the base (lower third) of the seminal vesicles bed (I.e., level of cut end of vas deferens) If SV invasion, include the entire seminal vesicle bed. Attempt to include existing surgical clips superiorly	1 cm above the pubic symphysis. In cases of pT3b disease: 3 cm above of the top of the pubic symphysis. Can be extended up to 4 cm in case of involvement of the last third of the SV. The inclusion of the posterior third of the bladder wall (with a thickness of 1 cm) is recommended.	1 cm above the pubic symphysis. In cases of pT3b disease: 3 cm above the top of the pubic symphysis

in the Clinic (QUANTEC) publications[2,43,89,90].

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- Alison Tree declares institutional research funding from Elekta, Varian and Accuray.
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CRediT authorship contribution statement

Matthew Warrender-Sparkes: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Jonathan M. Tomaszewski:** Writing – review & editing, Supervision, Methodology. **Christopher Ip:** Writing – review & editing, Methodology. **Sarat Chander:** Writing – review & editing. **David Christie:** Writing – review & editing. **Niall M. Corcoran:** Writing – review & editing. **Louise Emmett:** Writing – review & editing. **Renee Finnigan:** Writing – review & editing. **Amy Hayden:** Writing – review & editing. **Braden Higgs:** Writing – review & editing. **Patrick Horsley:** Writing – review & editing. **Tanya Holt:** Writing – review & editing. **Giuseppe Sasso:** Writing – review & editing. **Thomas P. Shakespeare:** Writing – review & editing. **Mark Sidhom:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Alison Tree:** Writing – review & editing. **Andrew Kneebone:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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