



## Time management: Improving the timing of post-prostatectomy radiotherapy, clinical trials, and knowledge translation

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### ARTICLE INFO

#### Keywords:

Prostate radiotherapy  
Adjuvant radiation  
Salvage radiation  
Journal club

### ABSTRACT

**Background:** Management of prostate cancer after surgery is controversial. Past studies on adjuvant radiotherapy (aRT) for higher-risk features have had conflicting results. Through the collaborative conversations of the global radiation oncology Twitter-based journal club (#RadOnc #JC), we explored this complex topic to share recent advances, better understand what the global radiation oncology community felt was important and inspire next steps.

**Methods:** We selected the recent publication of a landmark international randomized controlled trial (RCT) comparing immediate and salvage radiotherapy for prostate cancer, RADICALS-RT, for discussion over the weekend of January 16 to 17, 2021. Coordination included open access to the article and an asynchronous portion to decrease barriers to participation, cooperation of study authors (CP, MS) who participated to share deeper insights including a live hour, and curation of related resources and tweet content through a blog post and Wakelet journal club summary.

**Discussion of Results:** Our conversations created 2,370,104 impressions over 599 tweets with 51 participants spanning 11 countries and 5 continents. A quarter of the participants were from the US (13/51) followed by 10% from the UK (5/51). Clinical or Radiation Oncologists comprised 59% of active participants (16/27) with 62% (18/29) reporting giving aRT within the last 5 years. Discussion was interdisciplinary with three urologists (11%), three trainees (11%), and two physiotherapists (7%). Four months after the journal club its article Altmetric score had increased by 7% (214 to 229). Thematic analysis of tweet content suggested participants wanted clarification on definitions of adjuvant (aRT) and salvage radiotherapy (sRT) including indications, timing, and decision-making tools including guidelines; more interdisciplinary and cross-sectoral collaboration including with patients for study design including survivorship and meaningful outcomes; more effective knowledge translation including faster clinical trials; and more data including mature results of current trials, particular high-risk features (Gleason Group 4+, pT4b+, and margin-positive disease), implications of newer technologies such as PSMA-PET and genomic classifiers, and better explanations for practice pattern variations including underutilization of radiotherapy. This was further explored in the context of relevant literature.

**Conclusion:** Together, this global collaborative review on the postoperative management of prostate cancer suggested a stronger signal for the uptake of early salvage radiation treatment with careful PSA monitoring, more sensitive PSA triggers, and expected access to radiotherapy. Questions still remain on potential exceptions and

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<https://doi.org/10.1016/j.ctro.2021.07.003>

Received 7 July 2021; Accepted 26 July 2021

Available online 6 August 2021

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barriers to use. These require better decision-making tools for all practice settings, consideration of newer technologies, more pragmatic trials, and better use of social media for knowledge translation.

## Introduction

Prostate cancer is the second most common cancer and fifth leading cause of cancer death in men worldwide with 1,414,259 new cases and 375,304 deaths in 2020, and increasing [1]. Radical prostatectomy (RP) is a standard treatment for clinically localized prostate cancer, which may be followed by adjuvant (aRT) or salvage (sRT) radiotherapy for select patients [2,3]. However, optimal timing of post-operative radiotherapy is debatable. Is it better to offer radiotherapy before a PSA failure occurs, or to consider only after confirmed biochemical relapse?

Patients with locally advanced pT3 disease, a positive surgical margin of length >1 mm, or Gleason Grade Group (GG) of at least 4 have a higher risk for biochemical recurrence [4]. Previous randomised controlled trials (RCTs) by the Southwest Oncology Group (SWOG 8794), European Organization for Research and Treatment of Cancer (EORTC 22911), German Cancer Society (ARO 96-02/ AUO AP 09/95) and Finnish Radiation Oncology Group showed improvements in biochemical control in the aRT group compared to observation. Overall survival and metastasis free survival benefits were observed in SWOG 8794, but not in the other trials [5–8]. Amidst these results, aRT for patients with adverse pathological features has declined [9]. Hence, results from further clinical trials comparing aRT and early sRT such as RADICALS-RT have been eagerly anticipated to determine the standard of care after RP.

Twitter-based journal clubs are feasible and acceptable for convening a diverse global audience of health care providers from multiple disciplines and other public stakeholders to discuss and increase the impact of new research [10]. Moreover, qualitative methods such as focused conversations are increasingly used to explore complex health care topics. As such, the results of RADICALS-RT, an international phase 3 RCT in prostate cancer comparing an immediate postoperative (adjuvant) radiotherapy (aRT) and early salvage postoperative radiotherapy (esRT) policy was chosen for a collaborative review in the Radiation Oncology Journal Club (#RadOnc #JC) [11].

## Methodology

This Twitter #RadOnc #JC was held from 8AM (CST) on Saturday January 16, 2021 to 2 pm on Sunday January 17, 2021 in accordance with the usual protocol to encourage global diversity and facilitate inclusion [12]. The preparatory process included negotiating free access to the publication for the week of the chat [11]. A blog post provided a brief summary of the study's relevance and structured discussion topics (T1, T2, T3...Tn) for gentle appraisal (Supplementary: Table 3) [13]. Public tweets including the hashtag #pcsm for the prostate cancer community and infographics were sent periodically during the week before the chat. Select Twitter accounts for oncologists, surgeons, and patient advocates around the world were tagged to encourage balanced participation. The asynchronous portion started Saturday 8AM. The live hour occurred Sunday 1–2 PM. Moderation was by a resident (IP) and practicing physicians (MSK, RS, & HS). Lead discussants included the study's first author (CP) and chief statistician (MS). One Twitter poll was conducted on the use of adjuvant radiotherapy (Supplementary: Table 4).

After the journal club a social media analytics platform customized for healthcare (Symplur Signals [14]) was used to describe participant demographics. We organized tweets into a transcript using the social media content organization platform Wakelet and organized through thematic analysis [15]. As a measure of short-term change in attention, dissemination, and impact of the article, the baseline Altmetric

Attention Score was collected the week prior to the journal club on January 8, 2021 and on May 3, 2021 [16]. These results were used to guide a discussion on global practice implications and new lines of inquiry.

## Results

The journal club had 51 active discussants over the weekend share almost 600 tweets, participating from 10 countries from 5 continents. The discussion had 2.3 million impressions on Twitter (Table 1). There were 27 active participants whose input moved the discussion on the postoperative management of prostate cancer forward. Most active participants were from the US (48%) followed by the UK (18.5%). Most were physicians (85.2%), specifically radiation oncologists (51.9%).

A Twitter poll showed 62.1% (18/29) of participants gave aRT to patients for at least pT3 disease or a positive margin over the last 5 years, 34.5% did not, and the remainder could not recall (Supplementary: Table 4).

Four months after the journal club, the Article Altmetric Score had increased from 214 to 229 (7%) (Table 1).

We identified four key themes based on what participants felt was important for the postoperative radiotherapy management of prostate cancer since RADICALS-RT was published (Fig. 1). These themes included:

- 1. Clarification on Definitions:** guided by RADICALS-RT and longer-term results of pending trials, participants desired guidance on how aRT and sRT are defined. This included incorporation of newer definitions into guidelines and decision-making tools. It was understood that these aids should account for different practice environments including their resource constraints.
- 2. Increased Collaboration:** including more patient-reported outcomes in future trials, participation of other disciplines and patients in study design and interpretation, and more survivorship studies and development of interventions for long-term sequelae.
- 3. More Effective Knowledge Translation:** including more implementation of pragmatic trial designs for faster, more relevant integration into practice and newer techniques to improve accrual, assist with timely interpretation, and reduce bias.
- 4. Identification of Priority Areas for Further Study:** to better guide real-world application of RADICALS-RT results. Some participants expressed confidence that current evidence suggested a new standard of care of an early salvage policy (esRT) that included features traditionally used for aRT (GG4+, pT3b+, and margin-positive disease). However, others were hesitant to adopt this definition of sRT due to the limited long-term follow-up and representativeness of recent trials for patients with higher-risk disease or different practice settings given varying local patient and provider preferences including referral patterns, resource incentives, and constraints. For example, postoperative referrals to radiation oncology, multidisciplinary assessment, and tumor board discussions were described as more limited in the US compared to the UK. Other areas of uncertainty included the role of systemic treatments, treatment of pelvic lymph nodes, and dose-escalation with ongoing trials mentioned.

## Discussion

The #RadOnc #JC provided a collaborative review of the recent RADICALS-RT trial results on postoperative radiotherapy and further developed lines of inquiry.

**Table 1**  
#RadOnc #JC Twitter statistics, article altmetrics, and participants.

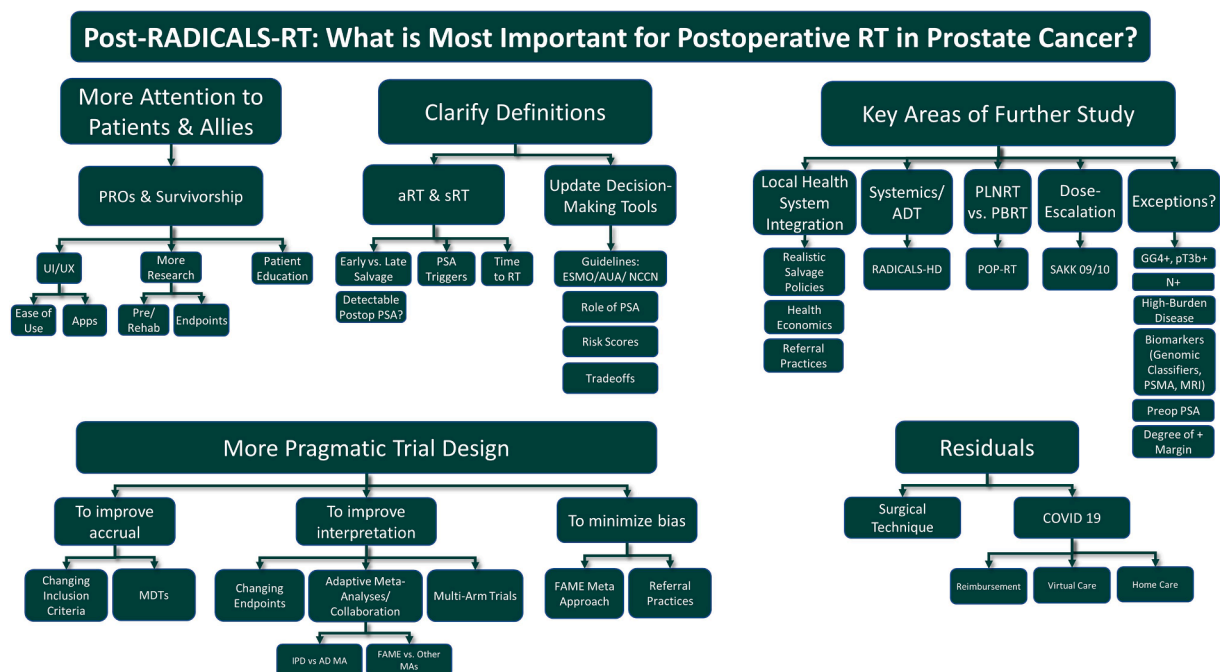
<b>Period: January 16 - 17, 2021</b>	<b>Total Continents: 5</b>	<b>Total Countries: 11</b>
<b>Impressions: 2,370,104</b>	<b>Participants</b>	
<b>Total Tweets: 599</b>	<b>North America: 14 (51.9%)</b>	<b>Total Participants: 51</b>
Unique Tweets 458 76.5%	US 13 48.2%	Active Participants 27 52.9%
With Mentions 407 67.9%	Canada 1 3.7%	Physicians: 23 85.2%
With Replies 252 42.1%	<b>Europe: 9 (33.3%)</b>	Clinical Oncologists 2 7.4%
With Links 88 14.7%	UK 5 18.5%	Radiation Oncologists 14 51.9%
With Media 79 13.2%	Spain 1 3.7%	Medical Oncologists 1 3.7%
Retweets 141 23.5%	Italy 1 3.7%	Residents 2 7.4%
<b>Altmetrics (January 10 -&gt; May 10)</b>	France 1 3.7%	Urology 3 11.1%
AAS 214 -> 229 7%	Belgium 1 3.7%	GP 1 3.7%
Citations 34	<b>South America: 1 (3.7%)</b>	Medical Students 1 3.7%
Captures 103	Chile 1 3.7%	Other Professors 1 3.7%
Social Media 249	<b>Australasia 2 (7.4%)</b>	Physiotherapists 2 7.4%
	Australia 1 3.7%	<b>Engagement Per Participant</b>
	New Zealand 1 3.7%	> 1 Tweet 51
	<b>Asia: 1 (3.7%)</b>	> 5 Tweets 12 24%
	India 1 3.7%	> 20 Tweets 7 14%

AAS = Article Altmetric Score; GP = General Practitioner; Active participants were defined as those providing tweet content pertinent to the discussion.

**Towards a safety culture**

Radiotherapy has a historical and ongoing variation in utilization. SWOG 8794 suggested improved metastasis-free and overall survival with aRT. During this time, the rates of aRT in the United States (USA) were low (9.9%) and unchanged from 2004 to 2011, due partly to skepticism of SWOG results and its trial design in the pre-PSA era and

very slow accrual [17]. Patients treated at high-volume surgical facilities were less likely to receive aRT compared with low-volume facilities (7.8% vs 15.9%; adjusted odds ratio 0.58 [95% confidence interval, 0.50–0.65]; P < 0.0001) and there was also less utilization according to race, lower income, and lower population density [17]. Similar patterns were noticed in Canada with 39% of appropriate patients being referred to radiation oncology for a discussion on aRT per guidelines and 20%



**Fig. 1.** Results of the thematic analysis of Tweets during the January 2021 #RadOnc #JC. PROs = Patient Reported Outcomes; aRT = adjuvant RT; sRT = salvage RT; UI/UX = User Interface & Experience; MA = Meta-Analysis; FAME = Framework for Adaptive MA; IPD = Individual Patient Data; AD = Aggregate Data; MDTs = Multidisciplinary Tumor Boards; PLNRT = Pelvic Lymph Node RT; WPRT = Whole Pelvic RT; PBRT = Prostate Bed RT.

receiving it [18]. Even for sRT where indications are stronger utilization was under 30% in Michigan, USA from 2012 to 2016 [19]. Although similar to the lower than clinically expected 33% of patients in SWOG 8794 (US/Canada) & EORTC 22911 (EU) in the observation arms who received sRT, it is much less than the 86% of patients in the Finn Prostate study (Finland) that received sRT (37/43). As such, this underutilization of radiotherapy is concerning.

Safety is a cornerstone of radiation oncology. Recently, radiation safety has received international attention with governments worldwide ratifying a World Health Organization (WHO) Global Action Plan on Patient Safety to mobilize resources, share knowledge, and facilitate coordination at all levels including a focus on health care institutions [20]. Standardization is widely recognized as an effective means to reduce errors and is used for global radiotherapy resource allocation. This does not mean textbook adherence to a single algorithm, but rather careful consideration of evidence-based standard options that may best fit patient, provider, and health system preferences and constraints. The journal club poll and analysis of content supported historical and ongoing variations in practice among oncologists worldwide with a possible majority (62%) preferring aRT for pT3+ or margin positive disease in the setting of an undetectable postop PSA. Further variation in the definitions for sRT included use in the setting of a detectable postop PSA, triggers for sRT, and the acceptable time period for salvage. For aRT, variations existed with indications, especially perceived utility for higher-risk disease (GG4+ or pT3b+) or patient populations with less access to early sRT. Workup (i.e. PSMA-PET, MRI, or Genomic Classifiers), treatment of pelvic nodal regions, and use of systemic agents also varied (Fig. 1). However, participants anticipated having these variations explained with the incorporation of RADICALS-RT and other pending trials into guidelines.

**Clinical guidelines may converge**

Clinical guidelines still vary. The European Society of Medical Oncology (ESMO) guideline states immediate postoperative radiotherapy after RP (aRT) is not routinely recommended [21]. This is supported by three RCTs (RADICALS-RT, RAVES and GETUG-AFU 17) [8,11,22]. On the contrary, the 2019 American Society for Radiation Oncology (ASTRO)/American Urological Association (AUA) guideline [23] emphasizes that patients with high risk pathologic features should be informed of the benefits of aRT because of improvements in

biochemical recurrence free survival and the 2021 US National Comprehensive Cancer Network (NCCN) guidelines suggest evidence supports offering it in these populations [24]. This decision is based on SWOG 8794, EORTC 22911, and ARO 96-02 [5–7]. As evidence and its interpretation matures so should clinical guidance based on local clinical needs.

**Clarifications of previous trials**

PSA has long been used as a marker and endpoint in all stages of prostate cancer. Previous RCTs consistently showed improved long-term biochemical progression free survival (bPFS) with aRT (Table 2). Participants highlighted common confusions in interpretation of PSA based on when it was measured (after RP, aRT, or sRT) and its level. For example, patients on an observation policy after prostatectomy may still be eligible for sRT after PSA failure to potentially improve survival and chance of cure, if it is detected before distant progression, offered, and received. After aRT, patients no longer have this option. Unlike distant metastasis-free survival (DMFS) as a validated surrogate endpoint [25], bPFS has not been shown to be a surrogate for harder endpoints such as overall survival (OS).

Results of SWOG 8794 and EORTC 22,911 differed. While SWOG demonstrated improved 15-year distant-metastases free survival (DMFS) for aRT (46% vs. 38% for observation) and OS (47% vs. 37% for observation) [26], EORTC showed no difference in 10-year rate of distant metastases (10.1% for aRT; 11% for observation) or OS (80%) [6].

Unlike subsequent trials, SWOG & EORTC included patients with a detectable postoperative PSA. This is now considered ‘PSA persistence’ with a known worse prognosis. In SWOG slightly more patients with PSA persistence (PSA > 0.2 ng/mL) received radiotherapy classified as ‘adjuvant’ (36% vs 28% of patients in EORTC). For both trials, median PSA at time of salvage was higher than conventional triggers (0.75 ng/mL in SWOG; 1.7 ng/mL in EORTC) and overall rates of sRT at 10-years was low (33% or 70/211 in SWOG; 164/502 in EORTC). Although still debated by participants, benefits of aRT seen in SWOG may have been due to its definition of aRT and lack of timely sRT.

**Radicals-RT**

Radiotherapy and Androgen Deprivation In Combination After Local

**Table 2**  
Relevant trials for postoperative radiotherapy in prostate cancer.

Clinical Trial	Inclusion Criteria	Arms	No. of patient	Median Follow up (Years)	Outcome	Toxicity
SWOG 8794 1988–1997	pT3 +positive margin/ ECE/SVI	aRT WS	425	>12	aRT improved DMFS (HR 0.71, 95% CI 0.54, 0.94) OS (HR 0.72, 95% CI 0.55, 0.96)	No difference at 5 years
EORTC 22911 1992–2001	pT2–3 +positive margin/ ECE/SVI	aRT WS	1005	10.6	aRT improved BPFS (HR 0.49, 95% CI 0.41–0.59) No difference in OS (HR 1.18, 95% CI 0.91–1.53)	Higher late toxicities in aRT, G3 ≤ 2%
ARO 96-02 1997–2004	pT3–4 +/-positive margin	aRT WS	388	9.3	aRT improved BPFS (HR: 0.51, 95% CI 0.37–0.70) No difference in DMFS, OS (not designed to report long term outcome)	G3 GU toxicities 1% in aRT
Finn Prostate group 2004–2012	pT2 + positive margin or pT3a	aRT WS	250	9	aRT improved BPFS (0.30, 95% CI 0.16–0.54)	Higher GI/GU/sexual function toxicities in ADT
RAVES 2009–2015	pT3 +positive margin/ ECE/SVI	aRT Early Salvage RT (PSA ≥ 0.20)	333	6.1	No difference in BPFS (HR 1.12, 95% CI 0.65–1.90) sRT did not meet trial specified criteria for non-inferiority	Higher ≥ G2 GU toxicities in aRT
GETUG-AFU 17 2008–2016	pT3 – 4 +positive margin	aRT Salvage RT	718		No difference in EFS (HR 0.81, 95% CI 0.48–1.36)	Higher GU toxicities, erectile dysfunction in aRT

Gleason Score (GS), Extracapsular extension (ECE), Seminal vesicle invasion (SVI), Adjuvant radiotherapy (aRT), Salvage radiotherapy (SRT), Radical prostatectomy (RP), Wait and see (WS), Event free survival (EFS), Gastrointestinal (GI), Genitourinary (GU).

Surgery (RADICALS-RT) was designed to address limitations of previous trials by comparing aRT and sRT with timely access to RT and carefully defined PSA inclusion and triggers for salvage. It was the largest RCT for the optimal timing of radiotherapy after RP for prostate cancer (n = 1396). RADICALS-RT enrolled patients with at least one risk factor (pathological T-stage 3 or 4, Gleason score of 7–10, positive margins, or preoperative PSA  $\geq 10$  ng/ml) between November 2007 and December 2016. Patients were assigned in a 1:1 ratio to adjuvant radiotherapy (aRT) or an observation policy with salvage radiotherapy (sRT) for PSA failure. In its recently reported results, at a median follow-up of 4.9 years there was no difference in bPFS (HR for aRT 1.10, 95% CI 0.81–1.49; p = 0.56). The definition of PSA failure was revised from that used in earlier trials to make a more appropriate comparison between arms. Freedom from non-protocol hormone therapy at 5 years was 93% with aRT versus 92% with sRT (HR 0.88, 95% CI 0.58–1.33; p = 0.53). Toxicity was more common with aRT. Most GI/GU events were of low severity. Grade 3–4 haematuria was 3% with aRT and < 1% with sRT during the first 2 years. Grade 3–4 urethral strictures were 6% with aRT and 4% with sRT (p = 0.020). The authors concluded an observation policy with early sRT for PSA failure was the current standard after RP.

#### Redefining PSA standards

RADICALS-RT was designed to test aRT against **early** sRT for PSA failure. In the previous trials, many patients in the observation arm did not receive timely salvage radiotherapy in the event of PSA failure. PSA failure after RP can be nuanced with various definitions cited in literature. AUA and the European Association of Urology (EAU) guidelines define biochemical recurrence as an initial PSA  $\geq 0.2$  ng/mL confirmed by two consecutive readings [27–28]. RADICALS-RT used a more sensitive trigger for salvage radiotherapy: (a) two consecutive rises and PSA  $\geq 0.1$  ng/mL or (b) three consecutive rises even if final PSA was < 0.1 ng/mL. RT was started within two months of randomization (aRT) or PSA failure (sRT). Journal club participants felt this was an improvement from previous trials.

#### Reclassifying postoperative risk

The majority of patients in RADICALS-RT were in a relatively favourable risk group. Gleason 3 + 4 disease was in 49%, 4 + 3 in 27%, and median PSA at diagnosis was 7.9 ng/mL (IQR 5.7–11.5 ng/mL). T-stage was pT2 in 24% and pT3a in 57%. PSA persistent patients were excluded. Strict PSA monitoring and salvage policies were followed. Most patients were also from the UK (82%) that has more concentrated geography than Ireland or Canada (over 3-times and almost 70-times respectively) and more universal healthcare than many other countries. Lack of access to PSA monitoring or early sRT in some populations may compromise the outcomes of a salvage policy. RADICALS-RT provided participants with reassurance that sRT is comparable to aRT for earlier endpoints with less toxicity, especially in certain populations.

Known features of poor outcomes post-prostatectomy were in a minority of studied patients. Similar to RAVES, median preoperative PSA in RADICALS-RT was < 10 ng/mL. While pre operative PSA was not reported in GETUG. Similar to both GETUG and RAVES, a minority of patients had pT3b seminal vesicle involvement (18.7% or 261/1396), pT4 disease (9/1396), Gleason Score 8 + in 17% (235/1396), or lymph node involvement (62/1396) [11]. However, as part of the study protocol the ARTISTIC collaboration performed an aggregate data meta-analysis that suggested no difference in the effect of these variables [29]. This provided more reassurance of greater applicability, although some participants still preferred waiting for more mature results from all three trials before accepting early sRT as standard in these populations.

The journal club discussed other emerging factors to further categorize risk. With improved pathologic and surgical techniques this included the extent of microscopically positive margins. Some participants suggested robotic surgery may influence the incidence of positive margins. A retrospective review and analysis reported less frequent positive margins in robotic-assisted laparoscopic

prostatectomy compared to conventional open RP (28.6% v 57.5%; P < 0.001) [30]. Other considerations were the impact of newer staging studies (e.g. MRI, PSMA-PET) or genomic classifiers to further refine post-prostatectomy risk and guide treatments.

#### Exploring radiotherapy details

During the journal club, participants debated factors other than timing that may influence postoperative radiotherapy outcomes, including optimal treatment volume, differing dose schedules, and using concurrent hormonal treatment.

#### Pelvic lymph node radiotherapy (PLNRT)

PLNRT remained contentious among participants. RADICALS-RT delivered aRT or sRT to the prostate bed. PLNRT could be added at the discretion of the treating oncologist, but was only used in 21 (3%) of 649 patients on sRT and 15 (7%) of 228 patients on aRT. In the intact prostate setting, a recent RCT from India (POP-RT) compared hypofractionated RT to the prostate (68 Gy/25#) to the same RT to the prostate with conventional RT to the pelvic nodes (50 Gy/25#) using image-guided IMRT. It accrued 224 patients from 2011 to 2017. Addition of PLNRT resulted in higher GU toxicity (17.7% vs. 7.5%, p = 0.03), but this was not reflected in patient-reported quality of life (QOL) [31]. GI toxicity was similar (6.5% vs. 3.8%, p = 0.39). Postoperative toxicities are expected to be higher. The older RTOG 0534 SPPORT trial that opened in 2007 showed higher acute grade 2 GI and bone marrow toxicities (p < 0.001) with PLNRT, with no increase Grade 3 GI/GU early or significant late toxicities [32]. Of note, unlike POP-RT, SPPORT allowed 3DCRT and port-film image guidance with PTV expansions from 6 to 15 mm. Results from both suggested improved outcomes, with POP-RT showing a 5-year bRFS of 95% with the addition of PLNRT (95% CI, 88.4 to 97.9) versus 81.2% (95% CI, 71.6 to 87.8) to the prostate alone (unadjusted HR of 0.23, 95% CI 0.10 to 0.52; P < 0.0001). Interestingly, addition of PLNRT also showed higher 5-year DFS (89.5% v 77.2%; HR 0.40; 95% CI, 0.22 to 0.73; P = 0.002) and DMFS (95.9% v 89.2%; HR 0.35; 95% CI, 0.15 to 0.82; P = 0.01). OS did not differ (92.5% v 90.8%, P = 0.83) [31]. Although PLNRT results are still maturing, they suggest tradeoffs that require further exploration.

#### Hypofractionation

Hypofractionation was discussed in the context of risk-reduction amidst the COVID19 pandemic and stressed resource constraints. A retrospective cohort study of 461 US patients compared hypofractionation radiotherapy and conventional fractionation (median dose 65 Gy at 2.5 Gy per fraction vs median dose 66 Gy at 1.8–2.0 Gy per fraction) [33]. This study suggested no difference in bPFS on multivariate analysis (HR 0.64, 95% CI 0.41–1.02, P = 0.059), or GI toxicity. There was increased late  $\geq 3$  GU toxicity at 6 years with hypofractionation (11% v 4%, p0.0081). Participants anticipated higher quality evidence from RADICALS-RT and other studies when available.

#### Hormone treatment (HT)

In RADICALS-RT, hormone treatment was under the discretion of the treating clinician or dictated by enrollment in RADICALS-HD where patients were allocated to HT for 0, 6, or 24 months. Three other RCTs (RTOG 9601, GETUG-AFU 16 and RTOG 0534) investigated HT with sRT. At a median follow-up of 13 years, RTOG 9601 showed improved OS with 24 months of bicalutamide versus placebo (HR for death 0.77, 95% CI 0.59 to 0.99; P = 0.04). There were also reductions in cumulative distant metastases (14.5% with bicalutamide v 23.0% with placebo, P = 0.005). Conversely, GETUG-AFU 16 showed no difference in 10-year OS, although this was with short-course androgen deprivation treatment with 6 months of goserelin (86%, 95% CI 81–89 v 85%, 95% CI 80–89 with RT alone, HR 0.93, 0.63–1.39; p = 0.73) [22]. Interim analysis of RTOG 0534 at median follow up 6.4 years reported a difference in freedom from progression (FFP) between salvage with prostate bed RT

+ PLNRT + 6-months of ADT at 89.1% versus 71.1% with sRT to the prostate bed only ( $p < 0.0001$ ) with longer term results pending [32]. In RADICALS-RT, 24% (154/649) assigned to the aRT group and 27% (61/228) in the sRT group were also assigned to receive HT [11]. Journal club participating oncologists and trainees eagerly anticipated results from RADICALS-HD which will provide clearer results between none, short-course, and long-course conventional HT.

### Tradeoffs

Expectedly, toxicity is more common with aRT. In RADICALS-RT, most RTOG toxicity was  $\leq$  grade 2. Grade 3 + GU/GI toxicity was  $< 5\%$  and  $< 1\%$  respectively. In the first two years post-randomization, grade 3 + urethral stricture was more common with aRT (39 [6%] v 30 [4%]). Patient-reported quality of life (QoL) was measured using validated Patient-Reported Outcome Measures (PROMs) suggested more GU/GI symptoms with aRT at one-year post-randomisation ( $p = 0.0023$ ). This difference resolved at 5-years ( $p = 0.073$ ,  $p = 0.084$ ), but compliance with PROMs was less complete at later timepoints. This increased toxicity with aRT was consistent with global QoL measures in SWOG 8794 that showed statistically significant increases in GU PROMs at 6 weeks and 2 years, but not at 5 years [5]. Sexual function was measured in RADICALS-RT and reporting is pending. The highest grade 3 + adverse event in the Finn Prostate Group study was erectile dysfunction with aRT (37% v 28%) and is expected to be similar [34]. Although RADICALS-RT did not perfectly fit all post-prostatectomy patient populations perfectly, and more mature outcomes are still pending, participants discussed the cost of this uncertainty in outcomes against the tradeoff of the known toxicity with aRT when deciding to accept sRT as a standard.

### Pragmatism in learning systems

Participants largely praised the RADICALS-RT trial team for their adaptive methodologies. RADICALS-RT opened in 2007 with disease-specific survival (DSS) as its primary endpoint. Shortly after, early results of SWOG 8794 suggested improved survival in post-prostatectomy patients due to advances such as the use of Docetaxel with the recognition of castrate-resistant disease and competing causes of death. Expected events decreased and to prevent delaying timely results beyond 10 years for the same statistical power the primary endpoint was changed to DMFS. Early results of RAVES and GETUG-17 then suggested a lower number of primary events doubling the expected necessary follow-up. Implementing collaborative practices including effective inter-trial communication, trial coordinators created the ARTISTIC collaboration with RAVES and GETUG-17, added the bPFS endpoint including PSA cutoffs to be able to relate, and organized a pre-planned adaptive aggregate data meta-analysis using established frameworks to minimize bias. Although different than traditional RCTs that face increasing criticism due to cost and lack of relevance once completed, this allowed actionable results to reach those who could benefit, sooner.

### Conclusion

This #RadOnc #JC journal club reviewed the landmark RADICALS-RT study that supports the use of salvage radiotherapy, deferring its potential toxicities until PSA recurrence after radical prostatectomy. Collaborative review suggested RADICALS-RT provided much needed data using contemporary definitions for adjuvant RT (aRT) and early salvage RT. Questions still remain regarding consideration of aRT in highly selected cases.. The global prostate cancer community awaits the longer-term results of RADICALS-RT and similar modern studies in this setting.

### 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.

### Acknowledgement

Matthew Sydes.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2021.07.003>.

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