Adjuvant Versus Early Salvage Radiation Therapy Following Radical Prostatectomy for Men with Localized Prostate Cancer

Robert T. Dess[1] · Todd M. Morgan[2] · Paul L. Nguyen[3] · Rohit Mehra[4] ·
Howard M. Sandler[5] · Felix Y. Feng[6] · Daniel E. Spratt[1]

Abstract Radical prostatectomy (RP) is now the most common definitive treatment for high-risk prostate cancer. Unfortunately, many men will have residual microscopic disease after surgery alone. Despite level 1 evidence supporting the use of adjuvant radiation therapy (ART), <10% of men with adverse pathology (positive margins or T3 disease) receive ART in the USA. Early salvage radiation therapy (eSRT) at the time of biochemical recurrence has been proposed as an alternative strategy despite the lack of published randomized trials to support this approach. Multiple randomized trials are ongoing or recently completed to compare ART to eSRT, but given the long natural history of prostate cancer, long-term oncologic outcomes from these trials will not be reported for several years. In this review, we discuss the shifting trends in the diagnosis of high-risk prostate cancer given a decline in PSA screening, use of RP for high-risk disease, and compare and contrast the retrospective and randomized evidence regarding ART and SRT.

Introduction

In 2013, the American Urological Association (AUA) and American Society of Radiation Oncology (ASTRO) issued a joint recommendation regarding a clinical framework for the use of radiotherapy (RT) after radical prostatectomy (RP). The panel stated, "Physicians should offer adjuvant radiotherapy [ART] to patients with adverse pathologic findings at prostatectomy including seminal vesicle invasion, positive surgical margins, or extraprostatic extension because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression" (Grade A recommendation) [1, 2]. Additionally, for men with a rising prostate specific antigen

✉ Daniel E. Spratt
sprattda@med.umich.edu

Robert T. Dess
rdess@med.umich.edu

Todd M. Morgan
tomorgan@med.umich.edu

Paul L. Nguyen
Paul_Nguyen@dfci.harvard.edu

Rohit Mehra
mrohit@med.umich.edu

Howard M. Sandler
Howard.Sandler@cshs.org

Felix Y. Feng
Felix.Feng@ucsf.edu

[1] Department of Radiation Oncology, University of Michigan School of Medicine, 1500 E. Medical Center Drive, Ann Arbor, MI 48109, USA

[2] Department of Urology, University of Michigan, Ann Arbor, MI, USA

[3] Department of Radiation Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

[4] Department of Pathology, University of Michigan, Ann Arbor, MI, USA

[5] Department of Radiation Oncology, Cedars Sinai, Los Angeles, CA, USA

[6] Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

(PSA) or local recurrence after prostatectomy, it was recommended that physicians should offer salvage RT (SRT). The recommendations to offer ART or SRT were to be "in the context of a thoughtful discussion of possible short- and long-term side effects of radiotherapy as well as the potential benefits of preventing recurrence". Additionally, AUA/ASTRO, along with American Society of Clinical Oncology (ASCO) [3] and European Association of Urology (EUA) [4], state that the benefits of SRT are greatest when administered at lower PSA levels.

Despite these recommendations, current practice patterns suggest that less than 10% of patients with adverse pathology receive ART [5–7]. Furthermore, and perhaps more concerning, for men who reach an undetectable PSA postoperatively (≤ 0.1) and then develop a rising PSA (≥ 0.1), studies suggest only approximately 30% receive SRT [7].

With decreased PSA screening and current trends of increased radical prostatectomy use in high-risk patients, the number of physicians and patients facing the decision between ART and early SRT will all but certainly grow. In this review, we discuss the available evidence for both adjuvant and salvage RT. Current ongoing randomized trials and potential future directions are highlighted. We conclude with our interpretation of the current most prudent strategy for the use of postoperative RT.

Radical Prostatectomy Trends: a Growing Need for Post-Operative Radiotherapy

A confluence of several factors has increased the percentage of patients with high-risk pathologic features following RP, thus expanding the eligible population for post-operative RT. First, in 2012, the United States Preventive Services Task Force (USPTSF) discouraged the use of PSA screening for prostate cancer [8], which has been effective in reducing the PSA screening rate in the USA [9]. As PSA screening rates have declined, recent data suggest that patients may be increasingly diagnosed with higher-risk disease [10].

In addition to the decline of PSA screening, practice patterns are changing. Historically, RP was primarily used in low-risk localized prostate cancer patients and RT was used in high-risk patients given the knowledge of the high failure rate after RP in patients with T3 disease. RP has become the most common definitive treatment modality for localized prostate cancer, and use of RP for those with high-risk disease has dramatically increased. In fact, recent data suggests that RP has now surpassed definitive RT as the most common modality for high-risk prostate cancer [11]. The driving force behind this pattern of care shift towards RP for high-risk disease is unclear. It is possible that recent advances in multiparametric magnetic resonance imaging, with its improved delineation of the prostatic and periprostatic tissues,

have increased surgeons' willingness and ability to pursue surgical resection [12]. Still others have suggested market forces may be, at least in part, at work given the association of higher socioeconomic status with receipt of RP [13], along with the increased dissemination of robotic surgical platforms [14].

Nevertheless, based on current estimates, approximately 30,000 men per year in the USA will have preoperative high-risk disease, of which 50% will undergo RP. There will also be thousands more with intermediate-risk disease that will get upstaged at the time of RP to have adverse pathologic features (Fig. 1). Unfortunately, based on nomograms from centers of excellence, such as Memorial Sloan Kettering, a large percentage of men (40–90%) with high-risk features, such as Gleason 8–10, high pretreatment PSA, T3 disease, or positive margins will have biochemical recurrence (BCR) following RP [17]. Even modern RP outcomes at specialized, high volume centers demonstrate significant rates of BCR in high-risk men, with some series exceeding 50% at 5 years [18, 19]. Therefore, we estimate that there will be approximately 15,000 to 25,000 men per year who develop recurrent disease following RP, which would make this entity about as common as pancreatic cancer, rectal cancer, esophageal cancer, multiple myeloma, or all brain tumors in men combined. Given the burden of this problem, it therefore comes as no surprise that several large trials have investigated the role of ART in those with adverse pathologic features following RP.

Adjuvant Radiation: the Level 1 Evidence

Three large, phase 3 randomized trials have been performed to test the hypothesis of whether or not adjuvant radiation offers an oncologic benefit in men with T3 disease or positive margins following radical prostatectomy: Southwest Oncology Group (SWOG) 8794, European Organization for Research and Treatment of Cancer (EORTC) 22,911, and the German Cancer Society ARO 96–02 (Table 1). With long-term follow-up, each trial met its primary endpoint and consistently demonstrated a reduction in the risk of BCR by approximately 50% with the use of adjuvant RT compared to observation [20–22]. Moreover, locoregional control was significantly improved in both the SWOG 8794 and EORTC 22911 trials.

The results of the two largest trials (SWOG and EORTC) are different with respect to the impact of ART on distant metastasis (DM). In the SWOG 8794 trial, ART was associated with an improvement in DM-free survival (hazard ratio (HR): 0.7, $p = 0.02$) and decreased the crude rate of distant metastasis (18 vs 9%). In contrast, EORTC 22911 reported no statistical difference in distant metastasis between the ART and observation (11.0 vs 11.3%, $p = 0.94$), and a lower overall rate of DM in the control arm than seen in SWOG 8794. Important differences should be noted between these trials.
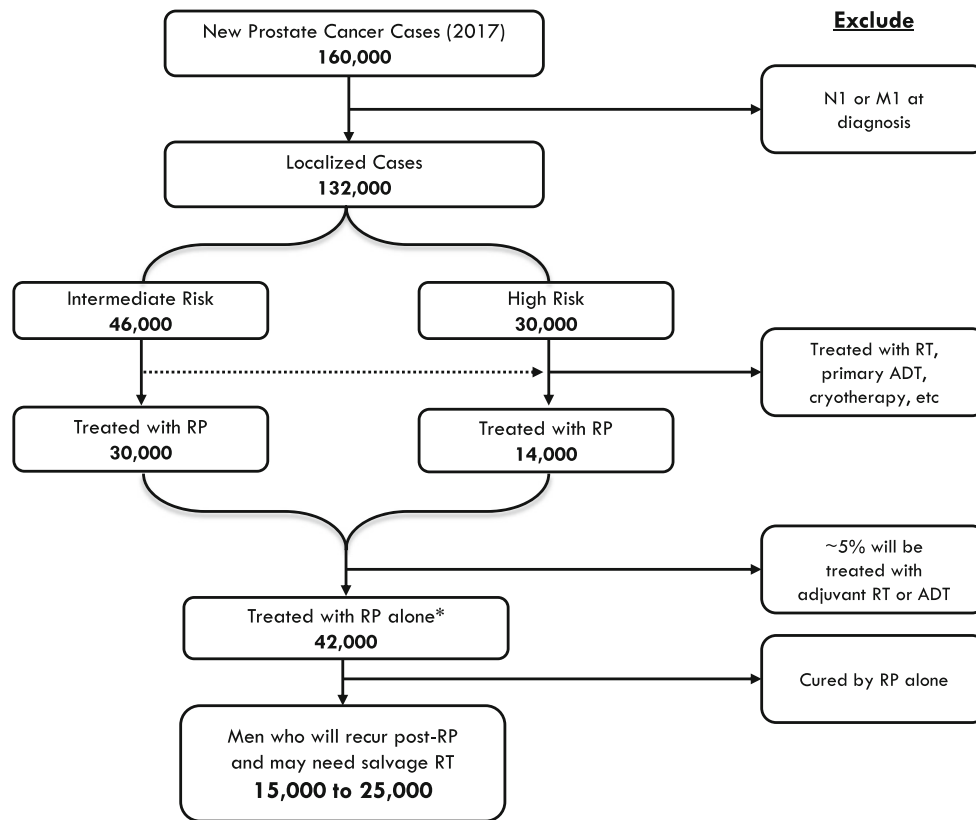
Fig. 1 Estimated cases of post-prostatectomy recurrences each year in the United States. *Asterisk* is the conservative estimated as it excludes low-risk patients from analysis assuming low-risk patients will not undergo immediate treatment. *RP* radical prostatectomy, *RT* radiotherapy, *ADT* androgen deprivation therapy. Estimates are based on the following: [5,10,11,13,15,16].

The proportion of patients with individual indications for ART (positive margins, extracapsular extension, or seminal vesicle invasion) was similar between the SWOG and EORTC trials; however, the SWOG trial had a greater proportion of men with all three factors (22 vs 12%). Furthermore, compared to the SWOG trial, patients on the EORTC study were followed more closely (every 6 months vs annually in years 4–5) and imaged more regularly (chest radiography and bone scans annually vs for symptoms only). While salvage RT was administered to men at similar rates in the observation arms of both trials (33%), it is possible that earlier, more effective salvage treatment was offered in the EORTC observation arm, and that the combination of a higher baseline risk population and infrequent monitoring led to an increased rate of metastatic disease in the SWOG observation arm. Of note, both SWOG 8794 and EORTC 22911 enrolled a substantial minority of patients with a detectable PSA (>0.2 ng/mL) prior to ART, 33 and 30%, respectively. This contrasts with the ARO 96–02 study which uniquely enrolled only men with an undetectable PSA (<0.1 ng/mL). Given its trial size (n = 315), however, the ARO study was not powered to detect a difference in distant metastasis.

Given the long natural history of prostate cancer, one must not only focus on cure but also on quality of life. Valid concerns exist regarding toxicity and the potential negative impact on quality of life when delivering multi-modality care, as ideally patients would be cured from their initial treatment. The EORTC 22911 trial recorded physician-reported outcomes and noted a small, but near-statistically significant increase in the 10-year cumulative incidence of grade 3 late toxicity with adjuvant RT compared to observation (5.3 vs 2.5%; $p = 0.052$). In contrast to physician reported outcomes, the SWOG 8794 investigators uniquely collected patient-reported outcomes, an important measure of quality of life [23] pertaining to urinary, bowel, sexual, and global domains for 5-year post-randomization. Moinpour et al. reported that early declines in urinary frequency as well as tenderness and urgency with bowel movements were significantly increased in the first 2 years following ART compared to observation [24]. Urinary frequency remained impaired over 5 years, but bowel function recovered by year 2 post-ART. Sexual function did not differ between ART and observation groups. Perhaps most strikingly, however, global

Table 1 Summary of randomized trials involving adjuvant or salvage radiation

Adjuvant radiation versus observation trials

Study	Years (n)	Inclusion criteria	Treatment arms	Median follow-up	PreRT PSA > 0.2	% Obs receiving salvage RT	bRFS	DM	DMFS	OS	% Salvage ADT	Toxicity
SWOG 8794	1988–1997 (n = 425)	pT3N0 or R1	60–64 Gy vs obs	12.6 years	33%	33% (median PSA of 1.0)	50 vs 25% HR: 0.4, p < 0.001	18% vs 9%	71 vs 61% (10 years) HR: 0.7, p = 0.016	74 vs 66% (10 years) HR: 0.7, p = 0.023	10 vs 21% (5 years)	Patient-reported global HRQOL improved with ART
EORTC-22911	1992–2001 (n = 1005)	pT3N0 T2 + R1	60 Gy vs obs	10.6 years	30%	33% (median PSA of 1.7)	62 vs 39% HR: 0.5, p < 0.001	10 vs 11% (10 years) HR: 0.99, p = 0.94	77 vs 71%	77 vs 80% (10 years) HR: 1.2, p = 0.20	10 vs 15% (5 years)	Late Gr3+ CI: 5 vs 3% p = 0.052
ARO-96-02	1997–2004 (n = 307)	pT3N0	60 Gy (3DCRT) vs obs	9.3 years	0%	NA	56 vs 35% HR: 0.5, p < 0.001	17 vs 14% p = 0.53	NR; underpowered	NR; underpowered	28 vs 31% (at 9.3 years) p = 0.42	3 vs 0% Gr3+ GU 0% Gr3+ GI

Salvage radiation plus hormonal therapy versus salvage radiation alone trials

Study	Years (n)	Inclusion criteria	Treatment arms	Median follow-up	PreRT PSA	High-risk features	PFS	DM	PCSM	OS	Toxicity
GETUG-16[b]	2006–2010 (n = 743)	pT2-T4a	66 Gy + 6 M goserelin vs RT alone	5.3 years	0.2–2.0 Median: 0.3 ≤ 0.5: 75%	T3: 46% SM+: 51%	80 vs 62% (5 years) HR: 0.5, p < 0.01	NR	NR	96 vs 95% (5 years) HR: 0.7, p = 0.18	No difference in acute or late Gr3
RTOG 9601[c]	1998–2003 (n = 760)	pT3N0 T2 + R1 PSA 0.2–4.0[a]	64.8 Gy + 24 M bicalutamide vs RT alone	13 years	0.2–4.0 Median: 0.6 0.7–4.0: 46%	T3: 67% SM+: 75%	HR: 0.5, p < 0.01 (12 yr. BCR CI: 44 vs 68%)	14 vs 23% CI (12 years) HR: 0.6, p < 0.01	6 vs 13% CI (12 years) HR: 0.5, p < 0.01	76 vs 71% (12 years) HR: 0.8, p = 0.04	No difference in acute or late Gr3

RT radiotherapy, bRFS biochemical recurrence-free survival, DMFS distant metastasis-free survival, OS overall survival, ADT androgren deprivation, PSA prostate specific antigen (ng/ml), HR hazard ratio, ART adjuvant radiotherapy, HRQOL health-related quality of life, BCR biochemical recurrence, CI cumulative incidence, Gr3 grade 3, GU genitourinary, GI gastrointestinal, 3DCRT 3D conformal radiotherapy. NR not reported, OBS observation, SM+ surgical margins positive, M months, Gy gray, DM distant metastasis, PCSM prostate-cancer specific mortality, PFS progression free survival

[a] Health-related quality of life and sexual function not assess in EORTC-22911. Sexual function not assessed on ARO-96-02

[b] Required post-operative PSA of ≤0.1 prior to PSA recurrence

[c] Study originally included patients only with PSA ≥ 0.5

health-related quality of life was significantly improved with ART compared to observation beginning after year 2 post-ART. This coincides with both the recovery of side effects from ART and the decreased likelihood of PSA recurrence, hormonal therapy, and distant metastasis in the ART arm.

A key take-home message is the fact that all three ART trials met their primary endpoint, and ART decreases BCR after RP for men with adverse pathology by approximately 50% compared to observation. There is potential that ART may also reduce DM based on the SWOG trial results. Additionally, ART causes a small absolute increase in toxicity in the first few years after treatment compared to observation, though long-term quality of life is minimally impacted, and if anything may be improved with ART given the reduction in recurrence. Based on this favorable level 1 evidence, one might conclude that an increased number of patients would receive ART. This has not occurred. Over the time span of these trials being conducted, followed, and reported, ART utilization in high-risk patients remained low and, if anything, declined: 9% in 2005 to 7% in 2011 [5]. Even young (<60) men with Gleason 8–10 disease with extraprostatic disease and a positive margin with no comorbidities still only received ART 33% of the time [5].

Given that a minority of patients with high-risk disease will have their disease eradicated with RP alone, and very few will be offered or receive ART, the importance of SRT becomes critical. SRT spares treatment in the patients with high-risk disease who remain disease-free following RP, and *may* be an alternative to ART if recurrences are local within the prostate bed where SRT is targeted.

The Wait-and-See Approach: Salvage Radiation as an Alternative Treatment Option

PSA is a sensitive marker for prostate cancer [25]. Natural history studies suggest that PSA recurrence following RP precedes DM often by greater than 5 years [26]. Upon PSA recurrence, older studies suggest that over 40% of blind biopsies will demonstrate evidence of local disease [27, 28]. Similarly, pelvic MRI imaging can detect evidence of local disease at time of PSA recurrence in up to 25% of patients [29, 30]. Moreover, evidence from the SWOG 8794 observation arm suggests that the most common pattern of failure following RP is local-only disease [31]. Empiric data suggest that upwards of 80% of men will have an initial response to SRT and many have long-term durable biochemical control [32], a finding not surprising based on

patterns of failure data. Furthermore, retrospective studies suggest that SRT reduces prostate cancer-specific mortality compared with other approaches [33, 34]. It is important to note, there has never been, nor will there likely ever be, a dedicated randomized trial comparing SRT to observation following RP.

Nomograms have been developed that demonstrate those men most likely to have durable, long-term biochemical control following SRT [35]. A contemporary update of the widely used "Stephenson nomogram" was recently published, now including nearly 2500 patients treated with SRT [36•]. One of the most prognostic factors of outcome after SRT that emerged from this study, and others, is the importance of the pre-SRT PSA. A growing body of literature has now found that early (PSA ≤ 0.5 ng/mL) or even "very early" (≤0.2 ng/mL) SRT not only has more favorable rates of biochemical control but also distant metastasis [37, 38]. In fact, those who receive SRT at a preRT PSA ≥ 0.5 can have upwards of >4 times the risk of distant metastasis compared to those with low preRT PSAs of ≤0.2 ng/mL.

As with ART, data suggests that SRT has been historically underutilized [39, 40]. This continues despite consensus recommendations supporting SRT [1, 2, 4]. In a statewide consortium of Michigan urologists between 2012 and 2014, only 30% of men received SRT for a post-prostatectomy PSA recurrence (≥0.1) [7]. And of those receiving SRT, over 40% had progressed to a PSA ≥ 0.5 and 20% progressed to a PSA ≥ 1.0 before SRT initiation. Several factors may contribute to this low rate of SRT. Retrospective studies suggest urinary incontinence can continue to improve for up to 2 years post-RP and there is concern that radiation may adversely impact post-operative healing [41]. Recent studies have examined the impact of SRT and its timing on health-related quality of life [42]. Similar to ART data, patients undergoing SRT have declines in bowel quality of life compared to those treated with RP alone without a lasting difference beyond 2 years. Moreover, patients with an interval greater than 7 months between RP and SRT had significantly improved sexual satisfaction and urinary function ($p < 0.05$), further encouraging a wait-and-see approach. Long-term overall quality of life were unchanged with SRT, again consistent with the ART experience. These transient quality of life concerns have merit. Unfortunately, the aforementioned data suggests a wait-and-see approach often equates to a wait-too-long approach.

Salvage Radiotherapy and Hormone Therapy

One of the primary concerns regarding the adoption of ART is the concern of overtreatment and potential side

effects. However, the discussion of use of ART versus SRT may no longer be simply comparing timing of radiotherapy, as SRT is going to be increasingly accompanied by potentially years of hormone therapy given the recent reports of two phase III trials comparing SRT to SRT plus hormone therapy (Table 1).

The first trial reported was the Groupe d'Etude des Tumeurs Uro-Génitales (GETUG)-AFU-16 trial, which demonstrated that the addition of 6 months of goserelin (androgen deprivation therapy) improved biochemical control but did not significantly lower distant metastasis rates or improve overall survival [43••]. The men treated on this trial were relatively favorable with 75% of patients having a pre-SRT PSA of ≤0.5 ng/mL and none were allowed to have persistently positive PSAs. The second trial, Radiation Therapy Oncology Group (RTOG) 9601, recently reported their long-term results [44••]. With a median follow-up of 13 years, the addition of 2 years of the nonsteroidal antiandrogen, bicalutamide, improved biochemical control, distant metastasis, prostate cancer-specific survival, and overall survival. This trial included men with markedly more aggressive disease than those in GETUG-16. RTOG 9601 should be viewed as a trial of men with high-risk features, as approximately 70% had T3 disease, 75% had positive margins, men had to have at least a pre-SRT PSA of ≥0.5 ng/mL to even enroll during the first one third of the trial enrollment period, approximately 50% had pre-SRT PSAs of 0.7–4.0 ng/mL, and a significant number had persistently positive PSAs. Notably, for men with low pre-SRT PSAs <0.7 ng/mL (a post-hoc hypothesis-generating cutpoint), low Gleason scores, or negative margins, there was minimal to no benefit from the addition of hormone therapy, and there was a concerning signal for worse overall survival in men with low pre-SRT PSAs likely given the side effects of long-term hormone therapy, including worsening cardiac disease [45].

The interpretation of these recent trial results is yet to be fully established, but most agree that for men with higher pre-SRT PSAs ≥0.7 ng/mL that the addition of 6–24 months of hormone therapy should be the standard of care, and that for men with more favorable features and lower pre-SRT, an informed discussion should be had about the risks and benefits of adding hormone therapy given that these men did not appear to derive an improvement in distant metastasis or overall survival. So when comparing ART to SRT, oncologists and patients alike must appreciate that SRT is now frequently going to be given with hormone therapy, which has a multitude of side effects, especially considering the poor oncologic outcomes with "late" SRT.

Data Comparing ART to SRT

It is important to emphasize that there are no reported randomized comparisons of ART to SRT, or observation

to SRT. Many retrospective comparisons have been performed [46–54]. Table 2 highlights select retrospective comparisons of ART and SRT. The studies selected for this table included studies with over 100 patients per group, an attempt to reasonably match ART and SRT cohorts, and at least 5 years of follow-up. Buscariollo et al. reported after performing propensity matching that ART was associated with a 6% absolute improvement in freedom from distant metastasis compared to "early" SRT as defined by receipt at a rising post-RP PSA level of ≤0.5 [48]. In contrast, Fossati et al. reported no significant difference in rates of distant metastasis when SRT was administered at post-operative PSA levels ≤0.5 when compared to ART [50]. Both of these studies demonstrated similar overall survival between ART and SRT, but none had a median follow-up greater than 10 years.

Comparisons such as those from Fossati et al. are reassuring, but limited in their practice changing utility given the inherent bias of retrospective comparisons. Fortunately, three randomized trials are ongoing or recently completed: Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS; NCT00541047), Radiotherapy Adjuvant Versus Early Salvage (RAVES; NCT00860652), and GETUG-17 (NCT00667069) (Table 2) [55–57]. A fourth, EORTC 22043, was terminated early due to poor accrual [58]. The RADICALS-RT trial is comparing ART with SRT, with the salvage trigger defined as two consecutive PSA > 0.1 or three consecutive rises. The primary endpoint is freedom from metastasis. RADICALS-HD is also separately testing the benefit of hormonal therapy by randomizing those receiving ART or SRT to 0, 6, or 24 months of hormone therapy. The primary endpoint of RADICALS-HD is cancer-specific survival. The RAVES trial is comparing ART versus SRT, and SRT is to be delivered within 4 months of a PSA ≥ 0.2. GETUG-17 is testing the non-inferiority of SRT versus ART with the SRT trigger PSA >0.2. Both ART and SRT are delivered with 6 months of hormonal therapy in GETUG-17.

The results of the above trials comparing ART to early SRT will help establish the new standard of care, but will near certainly require long-term follow-up to provide meaningful results. RTOG 9601 did not demonstrate an improvement in overall survival until the second decade of follow-up. Furthermore, even in RTOG 9601 relatively high-risk SRT population, there was still only a 5% prostate cancer-specific mortality 12-year post-treatment after SRT and hormone therapy, and clinically meaningful improvements will be challenging to demonstrate with such a low event rate. Therefore, it is highly likely that even if biochemical

Table 2 Summary of select retrospective and ongoing prospective trials comparing adjuvant and salvage radiotherapy

Select retrospective comparisons between adjuvant versus salvage

Study Details (Years, n)	Inclusion criteria	Analysis	ART Patients	ART RT	SRT Definition	SRT Patients	Pre-SRT PSA	RT	Outcomes (ART vs SRT) Median follow-up	bRFS	MFS	OS
Trabulsi et al. 2008[a] 1987–2002 ART: 211 SRT: 238	pT3-T4 post-RP PSA <0.2	192 Matched 1:1	Gl 8–10:18% SVI:24% PM:17%	Median: 60 Gy No ADT	Rising PSA > 0.2	Gl 8–10:18% SVI:24% PM:17%	Median: 0.7 Range: 0.2–2	Median: 64.8 Gy No ADT	94 vs 97 M (from RP)	75 vs 66% (5 years) p = 0.049 (from RP)	not reported	not reported
Ost et al. 2011[b] 1999–2009 ART: 144 SRT: 134	pT3 or PM post-RP PSA <0.2	178 Matched 1:1	Gl 7–9:28% SVI:26% PM:76%	Median: 74 Gy 54% ADT	Rising PSA > 0.2	Gl 7–9:28% SVI:25% PM:66%	<0.2: 0% 0.2–0.5:43% > 0.5: 57%	Median: 76 Gy 63% ADT	43 vs 60 M (from RP)	79 vs 68% (5 years) p = 0.04 (from RP)	95 vs 87% (3 years) p = 0.08 (from end of RT)	not reported

Select retrospective comparisons between adjuvant versus "early" salvage

Study Details (Years, n)	Inclusion criteria	Analysis	ART Patients	ART RT	SRT Definition	SRT Patients	Pre-SRT PSA	RT	Median follow-up	bRFS	MFS	OS
Buscariollo et al. 2016[c] 1992–2013 ART: 171 SRT: 230	pT3 or PM post-RP PSA <0.2	149 Matched 1:1	Gl 8–10:25% SVI:21% PM:83%	Median: 61.2 Gy 7% ADT	Rising PSA 0.1–0.5	Gl 8–10:26% SVI:24% PM:79%	Median: 0.3 IQR: 0.2–0.4	Median: 64.8 Gy 8% ADT	84 vs 106 M (from RP)	73 vs 49% (10 years) p < 0.01 (from RP)	96 vs 90% (10 years) p = 0.02 (from RP)	100 vs 99% (10 years) p = 0.50 (from RP)
Fossati et al. 2016 1996–2009 ART: 243 SRT: 267	pT3 post-RP PSA <0.1	Cohorts compared	Gl 8–10:27% SVI:44% PM:74%	Median: 60 Gy No ADT	Rising PSA ≤ 0.5	Gl 8–10:27% SVI:37% PM:52%	Median: 0.2 IQR: 0.1–0.3	Median: 67 Gy No ADT	94 vs 92 M (from RP)	not reported	92 vs 91% (8 years) p = 0.9 (from RP)	89 vs 92% (8 years) p = 0.9 (from RP)

Randomized trials of adjuvant versus salvage radiotherapy

Study Details Years (n)	Inclusion criteria	ART timing	ART dose	SRT timing	SRT PSA trigger	SRT dose	Primary endpoint
MRC RADICALS-RT (ART vs SRT) 2007- (n > 1000 planned)	1 of 4 adverse features[d]	Postop PSA ≤ 0.2 Within 6 M post-RP	66 Gy (or 52.5 in 20 fx)	Within 2 M	Two PSA > 0.1 or 3 rising PSA	66 Gy (or 52.5 in 20 fx)	Freedom from metastasis
MRC RADICALS-HD 2007- (n > 2000 planned)		if eligible for either ART or SRT, a second randomization 1) RT alone, 2) 6 months, or 3) 24 months of hormone therapy					Disease specific survival
TROG RAVES (ART vs SRT) 2009- (n = 470 planned)	pT3N0 or R1	Postop PSA < 0.1 Within 4 months post-RP	64 Gy	64 Gy	PSA ≥ 0.2 Within 4 M	64 Gy	bRFS PSA ≥ 0.4
GETUG-17 (ART + ADT vs SRT + ADT) 2007- (n = 718) pT3-4 N0 or R1	pT3-4 N0 or R1	Postop PSA < 0.1	66 Gy	66 Gy	PSA > 0.2 Before PSA >2.0	66 Gy	Event free survival

Select retrospective comparisons include studies with 100 patients per group, reasonably matched ART and SRT cohorts, and at least 5 years of follow-up

ART adjuvant radiotherapy, SRT salvage radiotherapy, RT radiotherapy, bRFS biochemical recurrence free survival, MFS metastasis-free survival, OS overall survival, PSA prostate-specific antigen (ng/ml), M month, Gl Gleason, SVI seminal vesicle invasion, PM positive margins, ADT androgen deprivation, RP radical prostatectomy, IQR intraquartile range, Gy gray, Fx fractions, M months

[a] Matched according to preoperative PSA, Gleason score, seminal vesicle invasion, surgical margin status, and follow-up from date of surgery.

[b] Matched according to preoperative PSA level, Gleason score, and pathologic T-stage.

[c] Matched according to age at surgery, surgery year, Gleason score, T-stage, and margin status.

[d] T3+, Gleason 7–10, preoperative PSA ≥ 10, or R1 resection

recurrence is improved with ART, it is less likely that distant metastasis and survival will be impacted without long-term follow-up.

Given the poor adoption of ART after three positive phase III trials and guidelines that support its use, it will be of interest of whether results from these trials comparing ART to eSRT will impact practice patterns. Clearly, future directions must focus on how to best personalize, optimize, and increase the utilization of ART and SRT for appropriate men.

Future Directions

Patient Selection: a Risk Adapted Approach

Not all men are at equal risk to develop clinically meaningful recurrence following RP. For example, post-hoc analysis after central pathologic review on the EORTC 22911 trial suggests that men with positive margins benefit most from ART [59]. In addition, pathologic specimens are heterogeneous. Men with higher Gleason scores at the margin, as well as those with longer linear lengths of margin positivity, are at higher risk of biochemical recurrence [60]. Moreover, investigators have demonstrated that pretreatment risk status informs post-operative biochemical recurrence risk [61] and others have noted that the number of pathologic risk factors increases risk of recurrence [62]. We suggest discussing the risks and benefits of ART with all men with T3 disease or positive margins as endorsed by AUA, ASTRO, and ASCO. Furthermore, we strongly encourage ART in men who have a Memorial Sloan Kettering Cancer Center or CAPRA-S nomogram predicted likelihood of progression after RP within 5 years of >50%, as the need for salvage therapy is very high and will likely be accompanied by additional therapies (e.g., hormone therapy or even docetaxel, as this chemotherapy is being tested in this setting).

Early Detection, Early Treatment: Use of Very Early Salvage Radiotherapy

The ART rate is <10% for men with adverse pathology, far from universal adoption. As we await the outcomes of the aforementioned ART versus SRT trials, the Urologic and Radiation Oncology communities should consider the emerging data supporting the advantages of very early SRT (pre-SRT PSA $\leq$ 0.2). Men with adverse pathology who do not receive ART should be followed closely (every 3 months) and counseled that the risk of distant metastasis increases substantially as their post-operative PSA rises [37]. Those who receive SRT at a preRT PSA $\geq$ 0.5 can be upwards of >4× risk of distant metastasis compared to those $\leq$0.2 [38]. Tests such

as ultrasensitive PSA may lead to further improvements in early detection of micrometastatic local recurrence and improve outcomes of SRT for patients with high-risk disease features [63, 64].

Improved Radiotherapy Targeting: Novel Molecular Imaging

Patient selection for SRT may be improved with novel molecular imaging. Such tests can help identify patients with local-only recurrences, locoregional recurrences (and thus warranting pelvic RT and or hormonal therapy), or metastatic recurrences. A 2016 meta-analysis of 68Ga-prostate-specific membrane antigen PET-CT demonstrated that the test can identify lesions in >50% of patients with biochemical recurrence and PSA levels of 0.2–1.0 [65]. Moreover, investigators from Emory are recruiting patients to test the role of FACBC (anti-1-amino-3-[18F] fluorocyclobutane-1-carboxylic acid (anti-3-[18F]), a synthetic amino acid analog, to guide post-prostatectomy decision and targeting (NCT01666808).

Biomarker Selection

Numerous genomic classifiers have been developed to provide patients and clinicians an improved understanding of a patients personalized risk of harboring aggressive prostate cancer and/or cancer that has a predilection to metastasize or result in death [66]. Recently, Spratt et al. reported the first meta-analysis of individual patient level and genomic level data on the genomic classifier Decipher [67]. Decipher independently predicts a patient's risk of distant metastases within essentially every demographic, clinicopathologic, and treatment subgroups. Decipher is utilized to stratify patients in the ongoing NRG GU-002 trial ("Phase II-III Trial of Adjuvant Radiotherapy and Androgen Deprivation Following Radical Prostatectomy With or Without Adjuvant Docetaxel"). Decipher is also being used in an ongoing, prospective randomized controlled trial, G-MINOR (Genomics in Michigan Impacting Observation or Radiation; NCT02783950). This trial randomizes patients with pT3 disease or positive surgical margins after prostatectomy to Decipher or control (CAPRA-S only) arms and is evaluating the impact of Decipher on utilization of ART and long-term oncologic outcomes in this setting.

Beyond the ability to prognosticate patients by risk of recurrence, genomic biomarkers have the potential to have predictive capacity to determine which patients specifically benefit from a treatment. The group from the University of Michigan recently developed a predictive 24-gene gene expression signature to determine who benefits most from post-operative radiation therapy, termed "PORTOS" [68]. Additionally, Feng et al. recently presented the results of applying a well-studied breast biomarker, PAM50, to

prostatectomy samples [69]. Not only did they find that PAM50 could identify luminal and basal subtypes but they also discovered that patients with luminal B cancers had improved response to post-operative hormone therapy compared to luminal A or basal subtypes. These exciting findings have sparked the first ever predictive biomarker stratified trial in radiation oncology for men with prostate cancer. This trial, NRG GU-006, is a randomized phase II trial comparing men receiving SRT with or without the second generation antiandrogen, apalutamide. Patients will be stratified by PAM50 molecular subtype.

Conclusion

Level 1 evidence supports the routine consideration of ART in men at high risk of local recurrence post-prostatectomy. Results from ongoing randomized trials will help to determine the role of early SRT compared to ART. Currently, data suggest both ART and SRT are underutilized, and when SRT is delivered, it is often delayed. The use of hormone therapy with SRT is evolving, and it is unclear if patients treated with early SRT, or a <10-year life expectancy, will derive a clinically meaningful benefit of hormone therapy. Ongoing and future clinical trials (NRG GU-006) will aim to better address this question. Looking to the future, imaging and genomic biomarkers will likely not only help in patient selection of post-operative radiotherapy but also to improve radiotherapy targeting. Given the history of poor adoption of level 1 evidence for patients receiving RP [19, 70–72], the largest challenge will be implementation of the results from the many ongoing and recently reported clinical trials in the post-operative space.

As we await the aforementioned randomized control trial results, it is our practice to recommend a multi-disciplinary discussion of the benefits and harms of ART for all men with T3 disease and/or a positive margin. Furthermore, Gleason grade can also impact a man's risk of recurrence, and we advocate utilizing publically available nomograms (e.g., Memorial Sloan Kettering) to personalize our recommendations of ART versus early SRT. Generally, men with T3 disease with a gross positive margin (not simply a focal positive margin) we recommend a strong consideration of ART, especially if they have a life expectancy over 10 years. Additionally, men who have a >50% risk of recurrence within 5 years of surgery we recommend ART over early SRT, as treatment will likely be more intensive with SRT (higher radiotherapy dose and often with hormonal therapy). Many of the authors also utilize genomic classifiers, such as Decipher, to further help personalize the use of ART, and recent nomograms have incorporated genomic and clinicopathologic risk to aid clinicians when genomic findings are discrepant with clinicopathologic findings [73].

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•• Of major importance

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