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Anatomical patterns of recurrence following biochemical relapse after post-prostatectomy salvage radiation therapy: a multi-institutional study

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Objectives

To characterise the frequency and detailed anatomical sites of failure for patients receiving post-radical prostatectomy (RP) salvage radiation therapy (SRT).

Patients and Methods

A multi-institutional retrospective study was performed on 574 men who underwent SRT between 1986 and 2013. Anatomical recurrence patterns were classified as lymphotrophic (lymph nodes only), osteotrophic (bone only), or multifocal if both were present. Isolated first failure sites were defined as sites of initial clinically detected recurrence that remained isolated for at least 3 months.

Results

The median follow-up after SRT was 6.8 years. The 8-year rates of local, regional, and distant failure for patients undergoing SRT were 2%, 6%, and 21%, respectively. Of the 22% men (128 of 574) who developed a clinically detectable recurrence, 17%, 50%, and 31% were lymphotrophic, osteotrophic, and multifocal, respectively. The trophic nature of metastases was prognostic for distant metastases-free survival (DMFS) and prostate cancer-specific survival (PCSS); the 10-year rates of DMFS were 18%, 5%, and 7% ($P < 0.01$), and PCSS were 78%, 68%, and 56% ($P < 0.01$), for lymphotrophic, osteotrophic, and multifocal failure patterns, respectively.

Conclusions

We demonstrate that trophism for metastatic site has significant prognostic impact on PCSS in men treated with SRT. Radiographic local failure is an uncommon event after SRT when compared to historical data of patients treated with surgery monotherapy. However, distant failure remains a challenge in this patient population and warrants further therapeutic investigation.

Keywords

radical prostatectomy, salvage radiotherapy, patterns of failure, #ProstateCancer, #PCSM

Introduction

Understanding patterns of treatment failure is critical in defining how best to further escalate or de-intensify therapy. In prostate cancer, the primary pattern of failure after definitive radiation therapy (RT) or radical prostatectomy (RP) is local. Despite the great concern for micrometastatic disease, even men who have high-risk prostate cancer most commonly recur locally, accounting for ~50% of all clinically detectable recurrences after RP or definitive RT [1–3]. Importantly, local control has been shown to correlate with the development of distant metastases (DM), as well as prostate cancer-specific survival (PCCS) [4–7].

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For men that choose to undergo RP for high-risk disease it is important to counsel them on the high recurrence rates after RP alone, with estimated 5-year rates of biochemical failure of 50–75% [8]. The use of adjuvant RT (ART) can reduce progression rates by 50% as reported in three randomised controlled trials [3,9,10]. However, the use of ART occurs in <10% of men who undergo RP who have high-risk features, and it is increasingly common for patients to undergo salvage RT (SRT) once they have biochemically recurred [11]. Given the increased use of RP for high-risk disease, and continued low rate of ART use, the patterns of failure in this setting are poorly described [12].

The patterns of failure after SRT are critical to better understand how to improve patient outcomes. For this reason, we aimed to characterise the patterns of failure after SRT and to determine if predominant trophic patterns of failure are prognostic for patient outcomes. In the present study, we report results of a large multicentre study assessing patterns of failure in a cohort of men treated with RP followed by SRT.

Patients and Methods

A multi-institutional study was performed on 574 men who underwent a RP with a standard pelvic lymph node dissection (PLND) and then received postoperative external beam SRT between 1986 and 2013. These men were selected from a cohort of 657 consecutively treated men receiving ART or SRT after RP. Excluding men whom received ART and those with positive pelvic lymph nodes (LNs) resulted in 574 remaining men. Analysis of these men was approved by local institutional review boards at all involved institutions.

All men were treated with external beam SRT with the use of either three-dimensional conformal RT or intensity-modulated RT. SRT was defined as post-RP RT delivered in the presence of a detectable PSA level (most common reason) or commencing at >4 months after RP. The clinical target volume was defined as the prostate bed. The planning target volume consisted of the clinical target volume plus a uniform 0.5–1.0 cm expansion, dependent on the use and modality of daily imaging. The median [interquartile range (IQR)] dose delivered to the planning target volume was 68.4 (64.8–68.4) Gy, delivered in daily 1.8 Gy fractions. Men with high-risk clinicopathological features were selectively treated to the pelvic LNs (19%, n = 23) and/or received neoadjuvant and concurrent androgen-deprivation therapy (ADT) (25%, n = 31), at the treating physician's discretion. If pelvic LNs were treated they received 45 Gy in 1.8 Gy daily fractions.

Endpoints

Clinically detected recurrences were discovered primarily through CT-based imaging or bone scintigraphy. LN recurrences were most commonly identified on CT-based imaging. LNs were considered suspicious if >8 mm in size in the pelvis or >10 mm in the retroperitoneum, or with abnormal shape (rounded), loss of a fatty hilum, inhomogeneity, or a clear increase in the size of a LN from prior imaging in the appropriate clinical context, such as a rising PSA level. All imaging was read by radiologists at one of the treating institutions; however, there was no repeat central review for this analysis. Imaging was typically performed at the time of post-RT biochemical recurrence, and then as clinically indicated following this (normally at least every 6 months for men with metastatic disease). The locations of first disease recurrence or metastatic site were grouped as local (prostate bed), confined to pelvic LNs (external and internal iliac, presacral, and obturator LN stations), retroperitoneal/abdominal LNs, thoracic LNs, bone, or viscera. An isolated site of first recurrence was defined as any recurrence limited to a single anatomical location in any of the above groupings for at least 3 months before discovery of additional sites of involvement, as proposed by Zumsteg et al. [2]. Men were also grouped based on their pattern of failure and were defined as having lymphotrophic, osteotrophic, or multifocal patterns of failure. All patients with visceral failures had multi-site failure, and as such are included in the multifocal pattern of failure. Lymphotrophic and osteotrophic patterns of failure were defined as metastatic disease confined to the LNs or bone alone, respectively, for at least 2 years from initial clinical detection before discovery of involvement of an additional site [2]. Patients with multiple anatomical locations involved within the first 2 years of a clinically detected recurrence were defined as having a multifocal pattern of failure. The time to a recurrence was defined as the time from the date of SRT to the date of the imaging study that identified radiographic evidence of recurrence.

Biochemical failure after SRT was defined as a rising PSA level of ≥0.2 ng/mL from the post-SRT PSA nadir, or any PSA level of ≥0.5 ng/mL. Prostate cancer-specific mortality (PCSM) was defined as a death in any man with progressive metastatic disease or castration-resistant prostate cancer. The time to development of metastases and PCSM was assessed from the time of biochemical failure after RP.

Statistical Analysis

Descriptive statistics were used to describe first sites of failure, as well as patterns of failure. Adjusted Kaplan–Meier methods controlling for patient age at the time of RT were used to assess DM-free survival (DMFS) and PCSS from the time of post-RP biochemical failure. A step-wise multivariate model was created using Cox-proportional hazards analysis for DMFS and PCSS. For all statistical analyses, two-tailed P values of ≤0.05 were considered statistically significant.

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS® version 21.0; SPSS Inc., Chicago, IL, USA) and MedCalc V16.4.3 (MedCalc Software, Mariakerke, Belgium).

Results

Patient Characteristics

The median (IQR) follow-up after SRT was 6.8 (3.9–10.2) years. The median (IQR) time from RP to SRT was 24 (11–49) months. Patient characteristics for the men who developed metastases can be found in Table 1; 74.2% of men had high-risk prostate cancer based on National Comprehensive Cancer Network (NCCN) criteria at the time of RP, 75.5% had Gleason Grade Group 3–5 (Gleason 4 + 3 to 10) disease [8,13,14], 69.9% were pathological stage T2b–T4, and the median (IQR) pre-RT PSA level was 0.7 (0.4–1.4) ng/mL.

In all, 128 of 574 men (22.3%) developed clinically detectable recurrent prostate cancer following biochemical recurrence after RP. No patient had a distant recurrence without a preceding biochemical recurrence. An additional three men had a local-only recurrence without developing metastases. The median (IQR) time to post-RP biochemical recurrence for these 128 men was 11.9 (5.0–24.8) months. The median (IQR) time from post-RP biochemical recurrence to development of metastases was 32.5 (11.4–64.2) months.

Table 1 Characteristics of the men developing post-SRT metastases.

Variable	Value
Median (IQR)	
Age, years	63.8 (57.7–68.2)
Pre-RP PSA level, ng/mL	7.0 (4.8–12.5)
Pre-SRT PSA level, ng/mL	0.7 (0.4–1.4)
SRT dose, Gy	68.4 (64.8–68.4)
ADT duration, months	6.6 (4.0–15.1)
N (%)	
Grade Group (Gleason score)	
1 (≤6)	6 (4.9)
2 (3 + 4 = 7)	24 (19.5)
3 (4 + 3 = 7)	41 (33.3)
4 (8)	19 (15.4)
5 (9–10)	33 (26.8)
pTstage	
T2a	37 (30.1)
T2b/c	46 (37.4)
T3a–T4	40 (32.5)
NCCN risk group	
Low	0
Intermediate	33 (25.8)
High	95 (74.2)
Positive surgical margins	56 (45.5)
Positive LNs	5 (4.7)
Pelvic nodal RT	23 (19.2)
Concurrent ADT	31 (25.2)

pTstage, pathological T stage.

Patterns of Isolated First Recurrences

Table 2 shows the sites of isolated first recurrences, as well as the total distribution of clinically detectable recurrences. In all, 104 patients developed an isolated first recurrence (i.e. disease located to a single site for at least 3 months). The most common site of isolated first failure was bone (63.5%), followed by retroperitoneal/abdominal LNs (12.5%), and then pelvic LNs (11.5%). Only one patient with an isolated pelvic LN failure received pelvic nodal irradiation. This was a left obturator LN failure and was within the RT field. Isolated local first failures were rare with five in total (4.8%).

Overall Patterns of Failure

From our entire cohort of 574 men receiving post-RP SRT the 8-year incidences of all anatomical sites of failure were calculated (Table 3) [2]. The 8-year actuarial rate of local failure was 2.2%, pelvic nodal failure was 6.0%, and distant failure was 21.0% (Fig. 1). Men with NCCN high-risk disease at RP had 8-year rates of local, regional, and distant failure of 2.5%, 6.2%, and 29.1%, respectively.

Metastatic Trophism and Impact on Outcome

The trophism of recurrences was able to be determined for 120 of the 128 men (93.8%) who developed metastases. In all, 62 men had osteotrophic disease (51.7%), 19 had lymphotrophic disease (15.8%), and 34 men had multifocal disease (28.3%). Men with multifocal disease had higher pre-RT PSA levels than men with lymphotrophic or osteotrophic disease, although this difference did not reach statistical significance; otherwise patient characteristics were similar between these three groups (Table S1). On further univariate analysis, the pre-SRT PSA level was not associated with either the trophic nature of metastases nor the development of isolated vs multifocal metastases when assessed as a categorical variable, with the commonly used thresholds of

Table 2 Distribution of clinically detectable recurrences.

Recurrence site	*Isolated first recurrence site - 104 patients with isolated first failure, *n* (%)	All clinically detectable recurrence sites - 238 total involved sites in 128 patients, *n* (%)
Local failure	5 (4.8)	13 (5.5)
Pelvic LNs	12 (11.5)	35 (14.7)
Retroperitoneal/ abdominal LNs	13 (12.5)	41 (17.2)
Thoracic LNs	3 (2.9)	15 (6.3)
Bone	66 (63.5)	102 (42.9)
Visceral	5 (4.8)	32 (13.4)

**Isolated first recurrence site defined as metastatic disease confined to a single location listed above for at least 3 months before involvement of a second site.*

Table 3 The 8-year cumulative incidence of all anatomical sites of failure.

Recurrence site	RP + SRT (Overall), %	RP + SRT (NCCN high-risk), %
Local failure	2.2	2.5
Pelvic LNs	6.0	6.2
Retroperitoneal/abdominal LNs	4.2	5.7
Thoracic LNs	1.9	2.6
Bone	12.3	17.7
Visceral	2.6	3.1
Overall 8-year incidence of local regional failure	8.2	8.7
Overall 8-year incidence of distant failure	21.0	29.1

Fig. 1 Cumulative incidence of all failures stratified by location (local, regional, or distant) for the entire cohort of men receiving post-RP SRT from time of SRT.

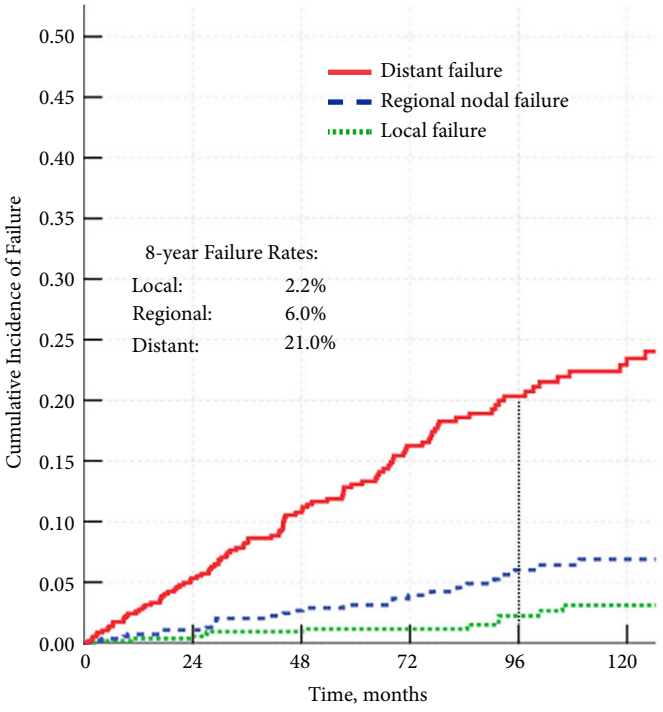
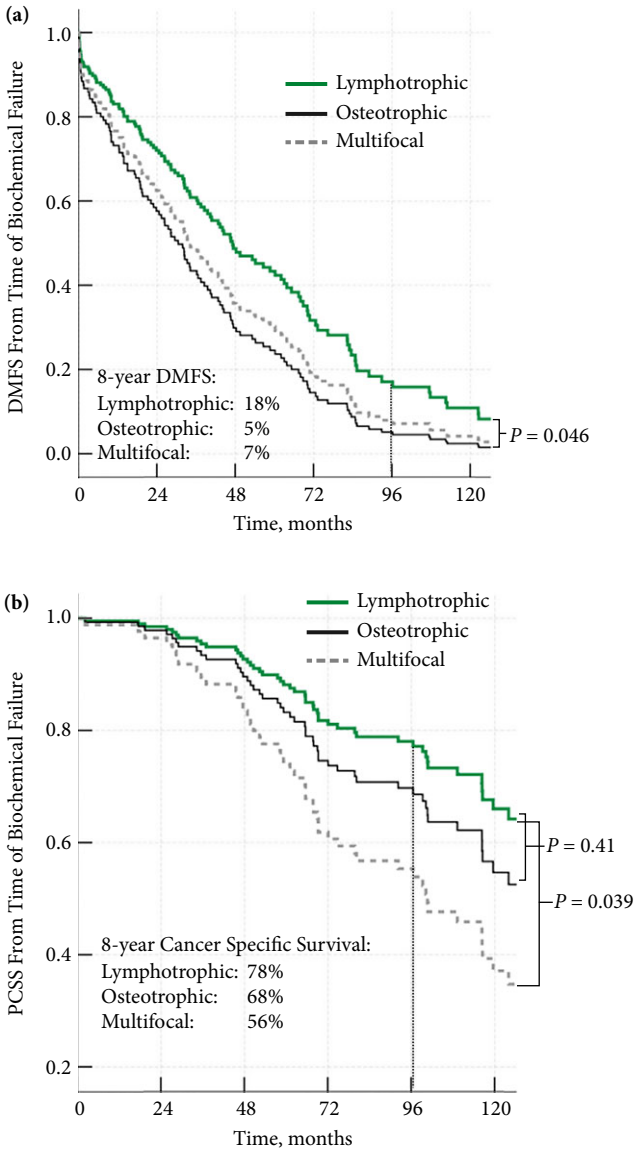


Fig. 2 Impact of trophic nature on (**A**) DMFS, and (**B**) PCSS from the time of biochemical failure after SRT.



0.2 and 0.5 ng/mL, nor as a continuous variable (all $P > 0.1$). The trophic nature of metastases was prognostic for DMFS and PCSS. The 10-year rates of DMFS were 18%, 5%, and 7% ($P = 0.046$, Fig. 2A), and PCSS were 78%, 68%, and 56% ($P = 0.039$, Fig. 2B), for lymphotrophic, osteotrophic, and multifocal failure patterns, respectively.

Lastly, we created multivariate models to assess for predictors of metastases and PCSM after SRT and biochemical recurrence, respectively. When assessing for predictors of metastases while controlling for Grade Group, pre-RT PSA level, surgical margin status, pathological T-stage, use of ADT during RT, and pelvic nodal irradiation (Table 4), retained variables in the model included: Grade Group 5 [hazard ratio (HR) 2.2, 95% CI: 1.4–3.5, $P < 0.001$], seminal vesicle invasion (HR 2.4, 95% CI: 1.5–3.6, $P < 0.001$), pre-SRT PSA level (HR 1.2, 95% CI: 1.1–1.3, $P < 0.001$), and the presence of a positive surgical margin (HR 0.4, 95% CI: 0.3–0.6, $P < 0.001$). When assessing for predictors of PCSM while controlling for Grade Group, recurrence trophism, pre-RT PSA level, surgical margin status, pathological T-stage, use of ADT during RT, and age (Table 4), the only variables retained in the model were Grade Group 5 (HR 2.4, 95% CI: 1.2–4.7, $P = 0.01$) and multifocal metastatic trophism (HR 2.1, 95% CI: 1.1–4.0, $P = 0.02$).

Table 4 Stepwise multivariable models

Model	HR (95% CI)	P
Model for DM from time of SRT		
Retained variables*		
Grade Group 5	2.2 (1.4–3.5)	<0.001
Seminal vesicle involvement	2.4 (1.5–3.6)	<0.001
Pre-SRT PSA level (continuous)	1.2 (1.1–1.3)	<0.001
Positive surgical margins	0.4 (0.3–0.6)	<0.001
Model for PCSM from the time of biochemical recurrence		
Retained variables†		
Grade Group 5	2.4 (1.2–4.7)	0.01
Multifocal metastases	2.1 (1.1–4.0)	0.02

**Variables entered but not retained: pT-stage, ADT use during SRT, pelvic nodal RT; †Variables entered but not retained: lymphotrophic, osteotrophic, Gleason Group 1–4, pre-SRT PSA level, positive surgical margins, pT-stage, ADT use during SRT, age.*

Discussion

In the present large multicentre study, with long-term follow-up, we have demonstrated multiple key findings that we believe are of interest to the urological oncology community. First, local failure is an infrequent event after SRT. Second, pelvic nodal failure, especially isolated pelvic nodal failure rates are uncommon, despite the omission of pelvic nodal RT in most patients and the lack of extended PLNDs in our present cohort. Third, distant failure appears to be the most common form of failure after SRT in contrast to surgery monotherapy or definitive RT. Finally, we validate that trophism for metastatic failure is prognostic for not only time to metastatic disease but also PCSS.

Local failure after RP monotherapy or definitive RT (±ADT) is the most common site of recurrence and is estimated to occur in 10–50% of patients based on pre-treatment characteristics. Furthermore, ~50% of all recurrences are local [1–3]. We demonstrate that when using two forms of local therapy (i.e. RP and SRT), as in our multicentre cohort, that only 5.5% of all recurrences had a local component to them. Furthermore, the cumulative 8-year radiographic local failure rate was only 2.2%. These data show the high efficacy of SRT to eliminate local disease, and as such, that further dose-escalation beyond 68.4 Gy is unlikely to result in demonstrable improvements in local control.

While surveillance CT imaging is a part of the standard of care for assessing men with recurrent prostate cancer, as done in our present study, it has been shown to have poor sensitivity and specificity in the detection of both local recurrence and LN metastases [15]. As such the true rate of both local recurrence and LN metastases in our present series is also likely underreported. Nonetheless, our very low 8-year pelvic LN recurrence rate (6.0%) suggests that these are not common occurrences for men receiving SRT. Furthermore, none of the patients in our present cohort received an extended PLND, and <20% of patients received pelvic nodal RT, which questions the potential benefit of elective pelvic nodal RT. Similar rates of pelvic recurrences have been reported from patients undergoing definitive RT without pelvic nodal RT, with 8-year rates of pelvic LN failure of ~4% [2]. However, the benefit of pelvic nodal RT in the salvage setting will definitively be answered by Radiation Therapy Oncology Group (RTOG) 0534, which is now closed and the data is maturing.

While local and regional control were excellent after SRT, development of metastases remained a common event with ~20% of the men in our present cohort developing metastatic disease by 8-years post-SRT. Furthermore, men with NCCN high-risk disease had nearly a 30% rate of DM at 8-years post-SRT. There are multiple potential explanations for these findings. First, these patients underwent SRT with a median time between RP and SRT of 24 months. This time interval potentially allows locally persistent disease to spread to regional or distant sites. This raises the question of whether ART may be ideal to not only achieve excellent local control, but also improve rates of DMFS by eradicating local disease before it can disseminate. This idea is supported by a detailed patterns of failure analysis of the Southwest Oncology Group (SWOG) 8794 randomised trial of RP ± ART, where at a median follow-up of 10 years only 7% of patients who received ART had developed metastases [1]. Patients in our present analysis also had a median pre-SRT PSA level of 0.7 ng/mL. Recent evidence suggests improved metastasis-free survival when men receive SRT when the PSA level is ≤0.5 ng/mL, and even further improved when the pre-SRT PSA level is ≤0.2 ng/mL [16,17]. As such, the elevated pre-SRT PSA levels in our present cohort may have in part contributed to the overall high rate of metastatic progression, and when possible we would recommend initiation of SRT at the time of biochemical recurrence before the pre-SRT PSA level elevated above 0.5 ng/mL and preferably with the pre-RT PSA level as close to 0.2 ng/mL as possible.

Another possible explanation for the high distant failure seen in our present analysis is that ADT was given to only ~25% of men, and ADT has been shown to be a potent radiosensitiser [18–20]. Additionally, prospective randomised trials (GETUG-AFU 16 and RTOG 9601) have recently shown improved progression-free survival with the addition of ADT to SRT, primarily in men with pre-SRT PSA levels of >0.7 ng/mL. Furthermore, RTOG 9601 has long-term follow-up and has shown improvement in DMFS and overall survival with the addition of ADT to SRT [21,22]. Our present study showed that men with Grade Group 5, pT3b, and a high pre-SRT PSA level all independently confirmed an increased risk for distant failure after SRT. Therefore, the addition of ADT should strongly be considered for men with any of these risk factors.

Other measures by which to decrease rates of DM in this setting are needed in addition to ADT. For men receiving postoperative RT, two prospective trials have shown the safety of docetaxel in combination with post-RP RT [23,24]. Preliminary results from

RTOG 0621, which assessed the addition of ADT and docetaxel after ART, showed improved progression-free survival compared to historical rates after ART alone [24]. Given the encouraging early results with docetaxel in combination with either definitive [25] or post-RP RT [24], and the high-rate of progression to metastatic disease for men receiving SRT, additional research is warranted assessing docetaxel or alternative systemic therapies in the context of SRT.

Despite the rigor in collecting our present data, there are multiple limitations that must be acknowledged. First, our present analyses are limited by their retrospective nature. Second, the use of MRI and more advanced functional imaging were not used, which have been shown to have increased sensitivity in detecting recurrent/metastatic disease [10]. Therefore, all of our present failure rates are probably underestimated. Additionally, biopsies of recurrent/metastatic sites were not taken to document true pathological evidence of prostate cancer. However, CT imaging and bone scans remain the standard of care imaging studies for men with recurrent/metastatic prostate cancer.

In closing, while local failures are rare after SRT these men remain at increased risk for progression to metastatic disease. As shown in recent randomised trials, the use of ADT in the setting should strongly be considered, especially for men with high pre-SRT PSA levels, and future clinical trials are needed to assess the possible benefits of treatment intensification with docetaxel, second generation anti-androgens, or other novel therapies, as well as companion biomarkers to better select patients for treatment intensification.

Conflicts of Interest

Daniel E. Spratt: Supported by the Prostate Cancer Foundation Young Investigator Award. Shuang G. Zhao: Supported by the Prostate Cancer Foundation Young Investigator Award. Travel/expenses: GenomeDx Biosciences. Howard M. Sandler: Consulting: Janssen, Medivation/Astellas, Sanofi, Ferring, Clovis Oncology, Varian. Rohit Mehra: Supported by the Prostate Cancer Foundation Young Investigator Award. Scott A. Tomlins: Advisory Boards: Medivation/Astellas, and Janssen. Grant funding: A. Alfred Taubman Medical Research Institute. Felix Y. Feng: Advisory Boards: Medivation/Astellas, GenomeDx, Nanostring, Celgene. Grant funding: Varian, Medivation/Astellas, Celgene. Todd M. Morgan: Advisory Boards: MDxHealth, Myriad Genetics. Research funding: MDxHealth, Myriad Genetics. Supported by the Prostate Cancer Foundation Young Investigator Award and by the A. Alfred Taubman Medical Research Institute.

References

1 **Swanson GP, Hussey MA, Tangen CM et al.** Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol* 2007; 25: 2225–9

2 **Zumsteg ZS, Spratt DE, Romesser PB et al.** Anatomical patterns of recurrence following biochemical relapse in the dose escalation era of external beam radiotherapy for prostate cancer. *J Urol* 2015; 194: 1624–30

3 **Bolla M, van Poppel H, Tombal B et al.** Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* 2012; 380: 2018–27

4 **Bill-Axelson A, Holmberg L, Garmo H et al.** Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med* 2014; 370: 932–42.

5 **Fuks Z, Leibel SA, Wallner KE et al.** The effect of local control on metastatic dissemination in carcinoma of the prostate: long-term results in patients treated with 125I implantation. *Int J Radiat Oncol Biol Phys* 1991; 21: 537–47

6 **Krauss DJ, Hu C, Bahary JP et al.** Importance of local control in early-stage prostate cancer: outcomes of patients with positive post-radiation therapy biopsy results treated in RTOG 9408. *Int J Radiat Oncol Biol Phys* 2015; 92: 863–73

7 **Zelefsky MJ, Reuter VE, Fuks Z, Scardino P, Shippy A.** Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer. *J Urol* 2008; 179: 1368–73

8 **Epstein JI, Zelefsky MJ, Sjoberg DD et al.** A contemporary prostate cancer grading system: a validated alternative to the Gleason score. *Eur Urol* 2016; 69: 428–35

9 **Thompson IM Jr, Tangen CM, Paradelo J et al.** Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* 2006; 296: 2329–35

10 **Pucar D, Sella T, Schoder H.** The role of imaging in the detection of prostate cancer local recurrence after radiation therapy and surgery. *Curr Opin Urol* 2008; 18: 87–97

11 **Morgan TM, Hawken SR, Ghani KR et al.** Variation in the use of postoperative radiotherapy among high-risk patients following radical prostatectomy. *Prostate Cancer Prostatic Dis* 2016; 19: 216–21

12 **Cooperberg MR, Carroll PR.** Trends in Management for Patients With Localized Prostate Cancer, 1990-2013. *JAMA* 2015; 314: 80–2

13 **Spratt DE, Jackson WC, Abugharib A et al.** Independent validation of the prognostic capacity of the ISUP prostate cancer grade grouping system for radiation treated patients with long-term follow-up. *Prostate Cancer Prostatic Dis* 2016; 19: 292–7

14 **Spratt DE, Cole AI, Palapattu GS et al.** Independent surgical validation of the new prostate cancer grade-grouping system. *BJU Int* 2016; 118: 763–9

15 **Hovels AM, Heesakkers RA, Adang EM et al.** The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. *Clin Radiol* 2008; 63: 387–95

16 **Abugharib A, Jackson WC, Tumati V et al.** Very early salvage radiotherapy improves distant metastasis-free survival. *J Urol* 2016; pii: S0022-5347(16)31206-X. doi: 10.1016/j.juro.2016.08.106. [Epub ahead of print]

17 **Stish BJ, Pisansky TM, Harmsen WS et al.** Improved metastasis-free and survival outcomes with early salvage radiotherapy in men with detectable prostate-specific antigen after prostatectomy for prostate cancer. *J Clinl Oncol* 2016; 34: 3864–71

18 **Goodwin JF, Schiewer MJ, Dean JL et al.** A hormone-DNA repair circuit governs the response to genotoxic insult. *Cancer Discov* 2013; 3: 1254–71

19 **Polkinghorn WR, Parker JS, Lee MX et al.** Androgen receptor signaling regulates DNA repair in prostate cancers. *Cancer Discov* 2013; 3: 1245–53

20 **Spratt DE, Evans MJ, Davis BJ et al.** Androgen receptor upregulation mediates radioresistance after ionizing radiation. *Cancer Res* 2015; 75: 4688–96

21 **Carrie C, Hasbini A, de Laroche G et al.** Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a

randomised, multicentre, open-label phase 3 trial. *Lancet Oncol* 2016; 17: 747–56

22 **Shipley WU**, **Pugh SL**, **Lukka HR et al.** NRG Oncology/RTOG 9601, a phase III trial in prostate cancer patients: anti-androgen therapy (AAT) with bicalutamide during and after salvage radiation therapy (RT) following radical prostatectomy (RP) and an elevated PSA. ASCO 2016 Genitourinary Cancers Symposium. *J Clin Oncol* 2016; 34(Suppl. 2S): abstr. 3

23 **Jackson W**, **Feng FY**, **Daignault S et al.** A phase 2 trial of salvage radiation and concurrent weekly docetaxel after rising PSA post-radical prostatectomy. *Int J Radiat Oncol* 2014;90:S431–S.

24 **Hurwitz MD**, **Zhang Q**, **Sartor O et al.** Adjuvant radiation, androgen deprivation, and docetaxel for high-risk prostate cancer postprostatectomy: results of RTOG 0621. *Int J Radiat Oncol* 2014;90:S2–S.

25 **Sandler HM**, **Hu C**, **Rosenthal SA et al.** A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521). ASCO 2015 Genitourinary Cancers Symposium. *J Clin Oncol* 2015; 33(Suppl.): abstr. LBA5002.

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Abbreviations: (A)(S)RT, (adjuvant) (salvage) radiation therapy; ADT, androgen-deprivation therapy; DM, distant metastases; DMFS, distant metastases-free survival; HR, hazard ratio; LN, lymph node; NCCN, National Comprehensive Cancer Network; PCSM, Prostate cancer-specific mortality; PCSS, prostate cancer-specific survival; PLND, pelvic LN dissection; RP, radical prostatectomy; RTOG, Radiation Therapy Oncology Group.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Patient characteristics by metastatic trophism.

