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Original Article

Prognostic factors in post-prostatectomy salvage radiotherapy setting with and without hormonotherapy: An individual patient data analysis of randomized trials from ICECaP database

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ABSTRACT

Background: Early salvage radiotherapy (SRT) is the standard of care for biochemical recurrence post-prostatectomy but outcomes are heterogeneous.
Objective: To develop a risk scoring system based on relevant standard-of-care clinico-pathological prognostic factors for patients treated with SRT with and without hormonal therapy (HT).
Design, setting, and participants: The Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) database included three randomized trials (Individual patients' data from 1647 subjects) assessing SRT (GETUG-AFU-16; NRG/RTOG-9601, and a subset of EORTC-22911).
Outcome measurements and statistical analysis: Outcomes were clinical progression (CP). metastasis free-survival (MFS) and overall survival (OS). Clinico-pathological factors, including pathological Gleason Score (GS), PSA at SRT start, margin status, persistent PSA post-RP and time from RP to SRT were evaluated by multivariable models stratified by type of treatment.
Results and limitations: On multivariable analysis PSA $\geq$ 0.5 ng/mL at SRT start, GS $\geq$ 8 and negative margin status were the three strongest prognostic factors. Three prognostic groups defined by number of these risk features (high risk: 2 or 3; intermediate risk: 1 and low risk: 0) were strongly associated with OS, MFS and CP outcomes with SRT alone or with HT. This prognostic group definition was also relevant for patients with persistent PSA post RP and for patients treated $<$ 1 year from RP to SRT and with and without HT.
Conclusion: A risk score for patients receiving SRT with or without HT, using three standard-of-care clinico-pathological risk factors provides refined prognostic information for individual patient counselling.
Patient summary: By using a composite score of pathology grading (Gleason Score), PSA at start of salvage radiation and margin status data, physicians can provide patients with more refined information on the risk of a second relapse after receiving radiation to the prostate bed after a prostatectomy for a rising or persistent PSA, both with and without hormonal therapy.

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Introduction

Well established and standard-of care clinicopathological variables associated with clinical outcomes after post-prostatectomy salvage radiotherapy (SRT) including pathological Gleason Score (GS), pre-SRT PSA, margin status, seminal vesicle involvement (SVI), post-operative PSA and PSA kinetics [1–4].

Numerous phase 3 trials and meta-analyses have assessed the benefit of the addition of hormonal therapy (HT) either as androgen deprivation therapy (ADT) with LHRH agonist or androgen receptor blockade with bicalutamide monotherapy, to post-operative radiotherapy. In general, the trials have shown clear improvements in PSA-based endpoints but variable impact on longer term endpoints such as MFS and OS [5–10]. We postulate the latter is due to variable inclusion of patients with a low versus higher risk of relapse and, in some reports, the inclusion of patients treated in the adjuvant setting. Given the heterogenous outcomes of this population, we leveraged individual patient data from randomized trials in the ICECaP repository to evaluate a risk scoring system with long-term clinical outcomes based on relevant standard-of-care clinicopathological prognostic factors for patients treated with SRT with and without hormonal therapy (HT).

The unique features of this current analysis are the following. First, we detail the frequency of the different risk factors across the key studies and report the low frequency of patients with poor risk features which influences the event-rate for MFS and OS events and power of the studies to define the benefits of HT. Secondly, we aim to evaluate a risk scoring system using standard of clinic-pathological. In addition, the analysis of the pooled data provides the opportunity to detail the outcomes of (i) patients with a persistently elevated PSA post prostatectomy and (ii) those who have a very early rise (within 1 year of surgery). The third unique feature is providing the most reliable estimates for the clinicopathological features associated with a very low risk of recurrence when treated with sRT alone. The fourth unique feature is providing estimates of 10-year outcomes which is relevant for men who are chosen for a prostatectomy.

Patients and methods

Patient selection

For this meta-analysis, we analyzed individual data of three major randomized trials, GETUG-AFU-16 [5], NRG/RTOG 9601 [6] and EORTC 22911 [11]. Patients that received SRT were included, which included the entirety of GETUG-AFU-16 and NRG/RTOG 9601, and a subset of patients in the EORTC 22911 who were randomized to the RP alone arm and received SRT at time of biochemical recurrence (Fig. 1; **suppl table 1**). Briefly, GETUG-AFU-16 and NRG/RTOG 9601 randomized patients receiving SRT with or without HT. The HT modalities were 6 months of LHRH agonist for the GETUG-AFU-16 trial and 150 mg bicalutamide for 24 months for NRG/RTOG 9601 trial. The GETUG study only included patients with delayed post-operative biochemical recurrence, whereas the RTOG study also included patients with a persistent post-operative PSA. The EORTC22911 trial [11] assessed the benefit of immediate post-operative radiotherapy versus a "wait and see" policy. Individual data from the subset of 155 patients out of the 503 patients randomized in the "wait and see" arm and subsequently had a PSA rise and received SRT without HT were included in this meta-analysis.

Endpoints

The primary clinical endpoints included clinical progression (CP) and MFS. The secondary endpoint was OS. CP was defined as the time from the date of randomization (or SRT initiation) to date of first evidence of local or regional progression, distant metastasis, or death from prostate cancer, while deaths from non-prostate cancer causes were counted as competing risks. MFS was measured from the date of randomization for GETUG-AFU-16 and NRG/RTOG 9601, or date of SRT initiation for EORTC22911, to date of first evidence of distant metastases on conventional scans or death from any cause; or censored at the date of last follow-up. OS was defined similarly as MFS, with death from any cause counted as events. The endpoint was censored at the date of

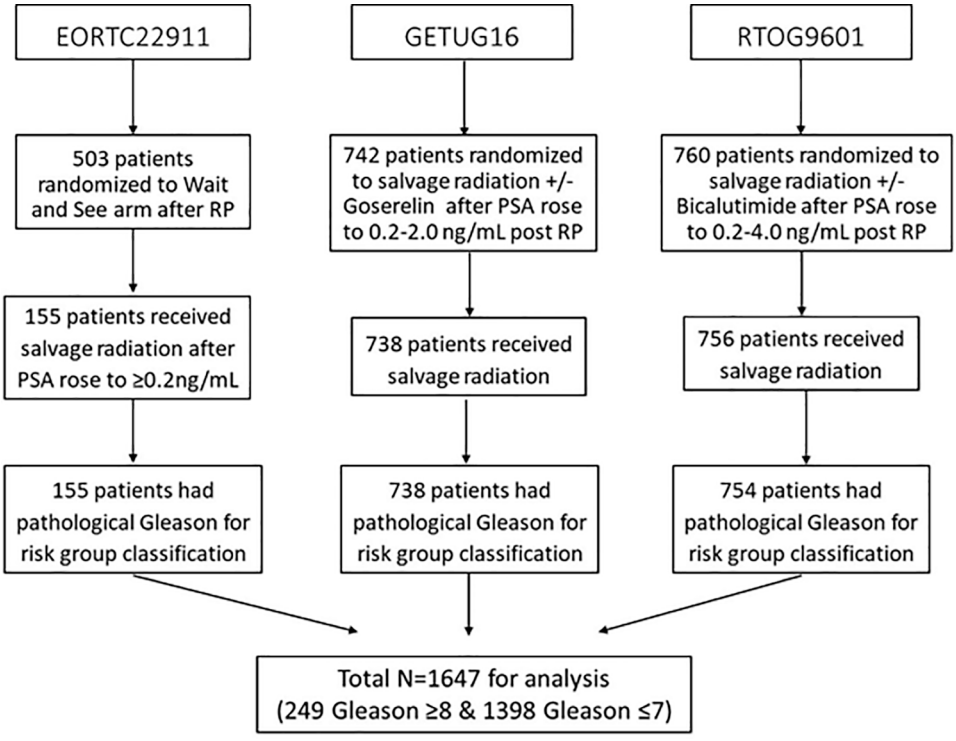

Fig. 1. Flowchart.

Table 1
Patient and Disease Characteristics (N = 1647).

	Overall population (N = 1647)
Age at SRT initiation (years), median (IQR)	66 (61–71)
PSA at SRT initiation (ng/mL), median (IQR)	0.50 (0.30–0.90)
Time from RP to SRT (years), median (IQR)	2.5 (1.4–4.3)
Time from RP to SRT less than 1 year, N (%)	
No	1413(86)
Yes	234(14)
PSA nadir post RP (ng/mL), N (%)	
<0.1	902 (55)
≥0.1	737 (45)
Unknown	8 (0.49)
Pathological Gleason Score, N (%)	
≤6	425 (26)
7	973 (59)
8–10	249 (15)
Pathological T stage, N (%)	
pT2	641 (39)
pT3-T4	849 (52)
Unknown	157 (10)
Positive margin, N (%)	
Yes	1041 (63)
No	604 (37)
Unknown	2 (0.12)
Seminal vesicle involvement, N (%)	
Yes	139 (8.4)
No	748 (45)
Unknown	760 (46)
Neoadjuvant hormone use, N (%)	
Yes	72 (4.4)
No	1575 (96)
Type of SRT, N (%)	
SRT alone	900 (55)
SRT + 6-month LHRH agonist	366 (22)
SRT + 2-year Bicalutamide	381 (23)

IQR: interquartile range, RP: radical prostatectomy, SRT: salvage radiotherapy.

last follow-up for patients alive and progression-free. PSA data was not uniformly available across all three studies to define PSA-based endpoints.

Statistical analysis

Five and 10-year MFS and OS estimates were determined by the Kaplan Meier methodology; CP at 5- and 10-year were estimated using cumulative incidence function accounting for competing risk. Univariate and multivariable Cox regression models (for MFS and OS) and the Fine and Gray competing regression (for CP) were performed to estimate the strength of association of clinical outcomes with pre-defined baseline risk factors, including pathological GS (≥8 vs. ≤7), post-RP PSA nadir (≥0.1 vs. <0.1 ng/mL), PSA at SRT start (≥0.5 vs. <0.5 ng/mL), margin status, age at SRT, and time from RP to SRT (≤1 vs >1 years). The multivariable models were also stratified by type of treatment (SRT alone, SRT + 6-month LHRH agonist, and SRT + 24 months of bicalutamide) to account for variability of treatments across the 3 trials.

PSA persistence after RP was defined as PSA ≥ 0.1 ng/mL after RP. PSA at SRT start was categorized to ≥0.5 vs. 0.5 ng/mL using the median as a threshold. The time from RP to SRT has been shown to be linked to PSA-doubling, with a median time from RP to SRT of 16.4 months for patients with a PSA-doubling time less than 6 months [3] and based on this report we chose SRT < 1 year from RP as potential proxy for PSA-doubling time and a poor prognostic group. PSA-doubling time could not be defined four this analysis due to lack of serial PSA datapoints for each patient in the database. Statistical analyses were performed using the SAS software application (version 9.4; SAS Institute, Cary, NC, USA). Two-sided p values < 0.05 were considered statistically significant.

Results

Key patient and treatment characteristics of the three trials used for the analysis are detailed in the flowchart (Fig. 1**)** and Table 1 **and** Supp-Table 2. A total of 1647 patients were available for this meta-analysis, with 155, 738, and 754 patients respectively from the EORTC 22911, GETUG-AFU-16 and NRG/RTOG 9601 (**Supp-Table 1**). Pathological GS was ≥8 in 15 % of the patients. Median PSA at SRT start was 0.5 ng/ml (IQR: 0.3–0.9). Overall, 55 % of the patients had an initially undetectable PSA (<0.1) post-RP (100 % in GETUG-16, 21 % in EORTC 22911, and 18 % in NRG/RTOG 9601). Median time from RP to SRT was 2.5 years (interquartile range (IQR): 1.4–4.3). 234(14 %) patients initiated SRT within 1 year post RP.

Overall, median follow-up was 10.5 years from randomization or SRT initiation (7.5; 9.4 and 13.1 years in EORTC22911, GETUG16, and RTOG9601, respectively).

Multivariable analyses of CP, MFS and OS with baseline factors are presented in Table 2. In multivariable models, pathological GS and PSA at SRT initiation were the two strongest prognostic factors for CP, MFS and OS (Table 2). Other notable findings from the MVA were the finding that a negative margin was also an adverse feature for clinical progression and MFS, but not for OS. Neither persistent PSA (>0.1 ng/mL post-RP) nor time from RP to SRT < 1 year were associated with any of the three endpoints.

Based on the results of the MVA, we then reported the outcomes by

Table 2
Multivariable regression for clinical progression, metastasis-free survival, and overall survival from randomization (SRT initiation) in whole population.

		Clinical progression (N = 1577*)		Metastasis-free Survival (N = 1621*)		Overall Survival (N = 1621*)	
Variables	**Levels**	**HR (95 % CI)****	**P-value**	**HR (95 % CI)****	**P-value**	**HR (95 % CI)****	**P-value**
Pathological GS	≥8 vs ≤7	1.82(1.41–2.36)	0 < .001	1.63(1.32–2.02)	0 < .001	1.49(1.15–1.93)	0.002
PSA persistence post-RP	≥0.1 vs <0.1 ng/mL	0.80(0.61–1.05)	0.12	0.96(0.77–1.20)	0.7	1.26(0.96–1.66)	0.090
PSA at SRT start, ng/mL	≥0.5 vs <0.5	2.10(1.64–2.68)	0 < .001	1.69(1.39–2.05)	0 < .001	1.68(1.33–2.13)	0 < .001
Margin	Negative vs positive	1.53(1.23–1.92)	0 < .001	1.41(1.18–1.69)	0 < .001	1.08(0.87–1.35)	0.5
Age at SRT initiation	Per year increase	0.99(0.98–1.01)	0.4	1.04(1.03–1.06)	0 < .001	1.08(1.06–1.10)	0 < .001
Time from RP to SRT	<1 vs ≥1 years	1.25(0.94–1.67)	0.12	1.15(0.90–1.46)	0.3	1.30(0.99–1.72)	0.062

CI: confidence interval, HR: hazard ratio, GS: Gleason score.

* Excluded 26 patients with missing data on risk factors for all endpoints. For clinical progression, 44 patients (from EORTC22911) who had local/regional progression prior to initiation of SRT were further excluded from the analysis.

** All models were stratified by type of treatment (SRT alone, SRT + 6-month LHRH agonist, and SRT + 2-year Bicalutamide) to account for variability of treatment across the 3 trials.

Table 3
Clinical progression, metastasis-free survival, and overall survival from randomization (SRT initiation) according to number of risk factors (GS 8-10, PSA at SRT start > 0.5 ng/mL and negative margin) in whole population.

	Total N	No. of events	5-year rate, % (95 % CI)	10-year rate, % (95 % CI)	Hazard Ratio (95 % CI)
Clinical progression (N = 1582*)					
0 risk factor	433	38	3.3(1.9–5.4)	8.3(5.7–11)	reference
1 risk factor	750	165	7.3(5.6–9.4)	19(16–22)	2.62(1.84–3.72)
2/3 risk factors	399	131	13(10–17)	30(25–35)	4.24(2.95–6.07)
Metastasis-free Survival (N = 1629*)					
0 risk factor	435	82	95(92–96)	83(79–87)	reference
1 risk factor	778	259	89(86–91)	71(68–74)	1.82(1.42–2.34)
2/3 risk factors	416	187	83(79–86)	59(54–64)	2.78(2.14–3.61)
Overall Survival (N = 1629*)					
0 risk factor	435	63	97(94–98)	89(85–91)	reference
1 risk factor	778	177	93(91–95)	82(78–84)	1.49(1.12–1.99)
2/3 risk factors	416	128	91(87–93)	74(69–79)	2.15(1.58–2.91)

CI: confidence interval, HR: hazard ratio.
* Excluded 18 patients with missing data on 3 risk factors for all endpoints. For clinical progression, 47 patients (from EORTC22911) who had local/regional progression prior to initiation of SRT were further excluded from the analysis.

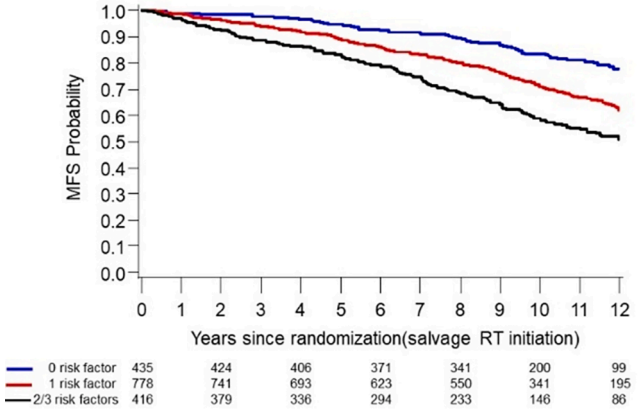

Fig. 2A. Kaplan Meier estimates of metastasis-free survival (MFS) according to number of risk factors (GS 8-10, PSA at SRT start >0.5 ng/mL and negative margin) in overall population.

the three endpoints (CP, MFS and OS) according to the number of (0 vs 1 vs 2/3) risk factors with the strongest association (other than age) on MVA with poorer prognosis: GS 8-10, PSA at SRT start > 0.5 ng/mL and negative margin in the whole population (Table 3 **and** Figs. 2A and 3A **respectively for MFS and CP**). Compared to patients with none of the risk factors, the presence of 1 or 2/3 risk factor(s) was strongly associated for CP, MFS and OS, and defined a high (2/3), intermediate [1] and low risk group (no risk factor) in this cohort.

A subgroup analysis was performed in patients with persistent PSA (≥0.1 ng/mL) post RP (**Sup Table 3 and 4 and** Figs. 2B and 3B respectively **for MFS and CP**) and for patients with <1 year between RP and SRT (**Sup Table 5** and Figs. 2C and 3C respectively for MFS and CP). Similar results were observed with a significant impact of the risk groups defined above on CP, MFS an OS in patients with persistent post-RP PSA and for patient with initiation of SRT < 1 year from RP. For patients with persistent PSA post RP, in addition to GS ≥ 8, PSA at SRT > 0.5 and negative margin, time from RP to SRT < 1 year was also an adverse factor for CP, MFS and OS.

Notably, the prognostic information associated with the three risk

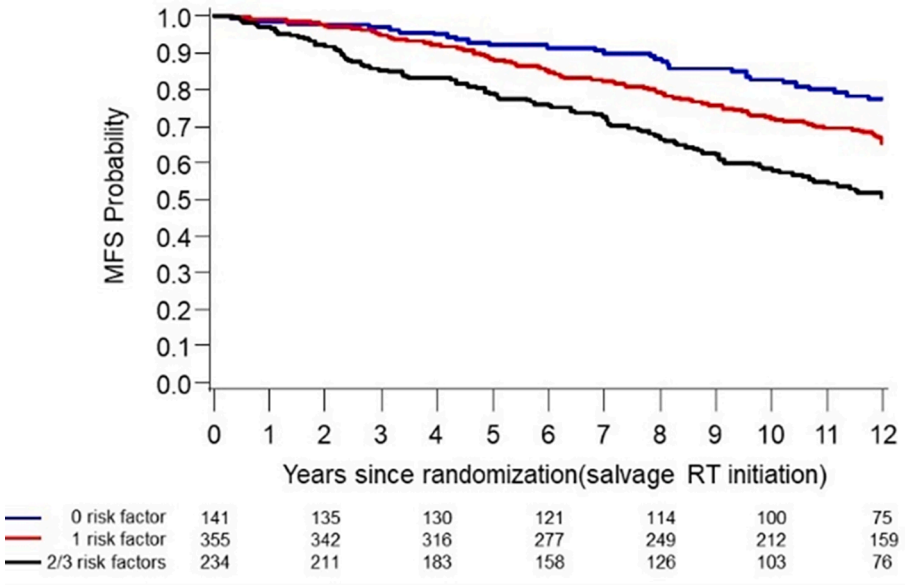

Fig. 2B. Kaplan Meier estimates of metastasis-free survival (MFS) according to number of risk factors (GS 8-10, PSA at SRT start >0.5 ng/mL and negative margin) in patients with persistent PSA post RP.

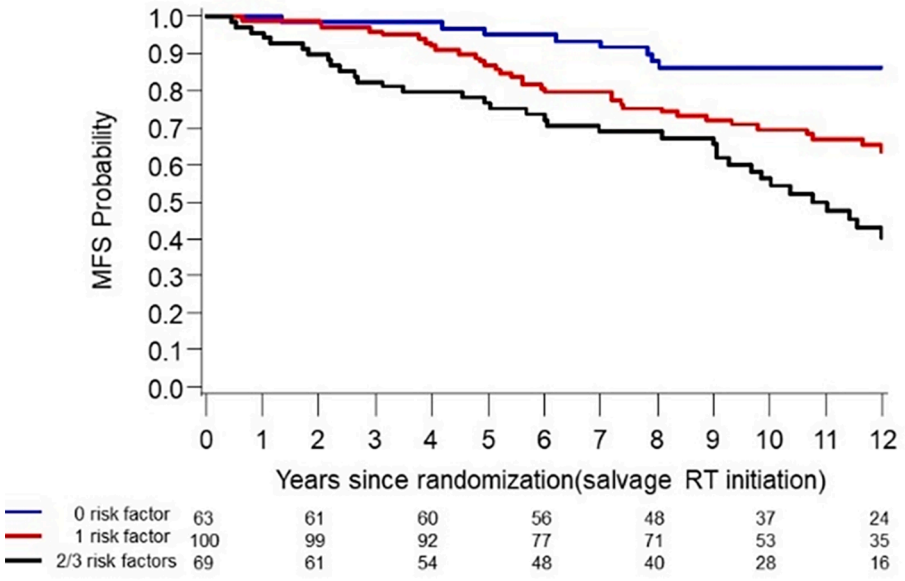

Fig. 2C.

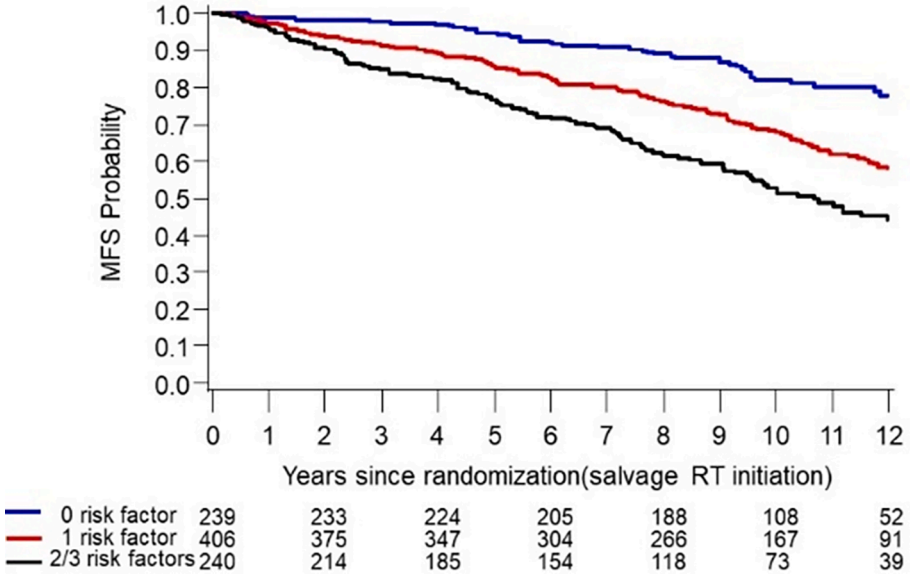

Fig. 2D. Kaplan Meier estimates of metastasis-free survival (MFS) according to number of risk factors (GS 8-10, PSA at SRT start >0.5ng/mL and negative margin) in patients receiving SRT alone.

groups was also consistent for CP, MFS and OS according to the treatment modality: SRT alone; SRT + 6 months LHRH agonist and SRT + 2-years Bicalutamide (Supp Table 6 & 7, Figs. 2D-E-F and Figs. 3D-E-F respectively for MFS and CP) and in each trial (Supp Table 8**).** Interestingly the risk groupings were particularly discriminative for all clinical endpoints at 10-years when considering SRT alone and outcomes were consistently more favorable with addition of HT **(**Supp Table 6 and 7**).**

Discussion

Consistent with previous reports [1–3], and a recently published systematic review [4] pathological GS, pre-SRT PSA and negative margin status are the three major prognostic factors for patients treated with SRT. Moreover, we detail the compound worsening of prognosis with presence 0 to 1 to 2/3 of these risk factors. Reassuringly, this more granular data can be obtained with readily available standard-of-care clinico-pathological variables and does require waiting months to determine a patient's PSA doubling time.

In addition, for patients treated with SRT alone across all three trials we detail the relatively low frequency (approximately 25 %) of patients with 2 or 3 RF with an MFS of 53 % at 10-years versus approximately 50 % of patients with 1 RF with a 10-year MFS of 68 % and 25 % with 0 RF with an a 10-year MFS of 82 % (Fig. 2D, Sup Table 7). As such the event rate and inherent power is quite low for each individual trial to detect MFS (as surrogate for OS) or a direct OS benefit from adding HT to SRT, especially if reliant 5-year endpoint. This information likely explains the inconsistent reports from randomized phase 2 and 3 trials [5,7–97,13]. For instance, the RADICALS trial which include patients treated in adjuvant and salvage setting and with low and poor risk factors did not demonstrate a benefit in terms of MFS with 6 months HT versus sRT alone, but a 6 % gain comparing 6 versus 24 months HT [8,9]. Given the

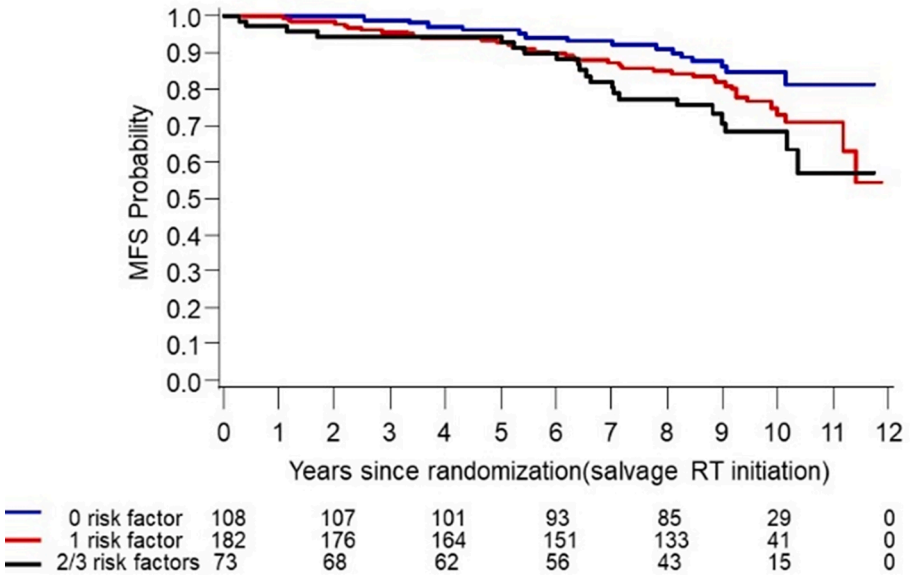

Fig. 2E. Kaplan Meier estimates of metastasis-free survival (MFS) according to number of risk factors (GS 8-10, PSA at SRT start >0.5 ng/mL and negative margin) in patients receiving SRT + 6-month LHRH agonist.

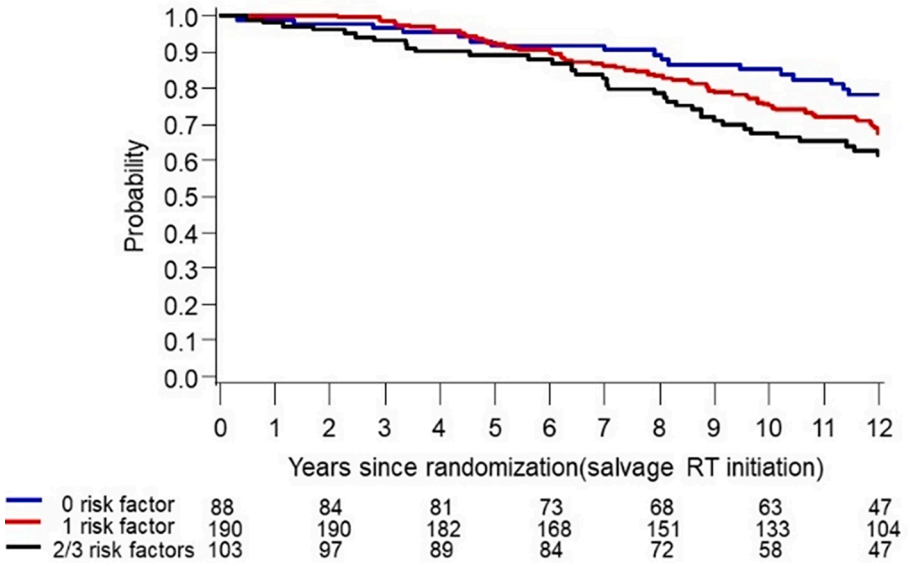

Fig. 2F. Kaplan Meier estimates of metastasis-free survival (MFS) according to number of risk factors (GS 8-10, PSA at SRT start >0.5 ng/mL and negative margin) in patients receiving SRT + 24 months Bicalutamide.

variable patient mix and disparate findings we propose the risk scoring systemic derived from this analysis can be used as preliminary data to guide both future with in-study subgroup analyses of completed trials or individual patient data meta-analysis which includes more recently completed SRT trials to define which patients benefit most from adding HT to SRT.

In the subset of patients with PSA persistence, SRT < 1 year from RP was associated with poorer CP, MFS and OS (Sup Table 3). Due to most patients (67 %,119/177) receiving SRT < 1 year from RP also having pre-SRT PSA ≥ 0.5 ng/mL, there were too few patients to reliably create a separate risk model to incorporate SRT < 1 year from RP as a risk factor for patients with PSA persistence.

In a recent analysis based on a large multinational database, Tilki at al demonstrated that PSA at SRT start > 0.25 ng/ml (and undetectable post RP PSA) was associated with poorer outcomes [14]. In our whole population, the majority of patients (82 %) had PSA at SRT start > 0.25 ng/mL, as the trials only enrolled patients with baseline PSA > 0.2 ng/mL. Using the median as a threshold, we demonstrated that PSA > 0.5 ng/mL was a strong prognostic factor for all the outcomes we analyzed, regardless whether PSA was persistent or not post RP. This cut-off of pre-SRT PSA > 0.5 also had a prognostic negative impact in the GETUG trial [5].

There are several limitations of our study. There were variable PSA levels as entry criteria to the studies and lack of complete data from all three trials for prognostic factors such as seminal vesicle status, pathological T-stage and nodal status. As serial PSA data prior to SRT was not uniformly available for our current analysis and we were not able to account for the PSA kinetics. Instead, we reported SRT < 1 year from RP as a surrogate for a rapid PSA doubling time post RP/rapid relapse, based on published data [3]. We have not analyzed time from RP to SRT as a continuous variable as the output could not be included in a simple risk score. Data from the EORTC study are not directly from the

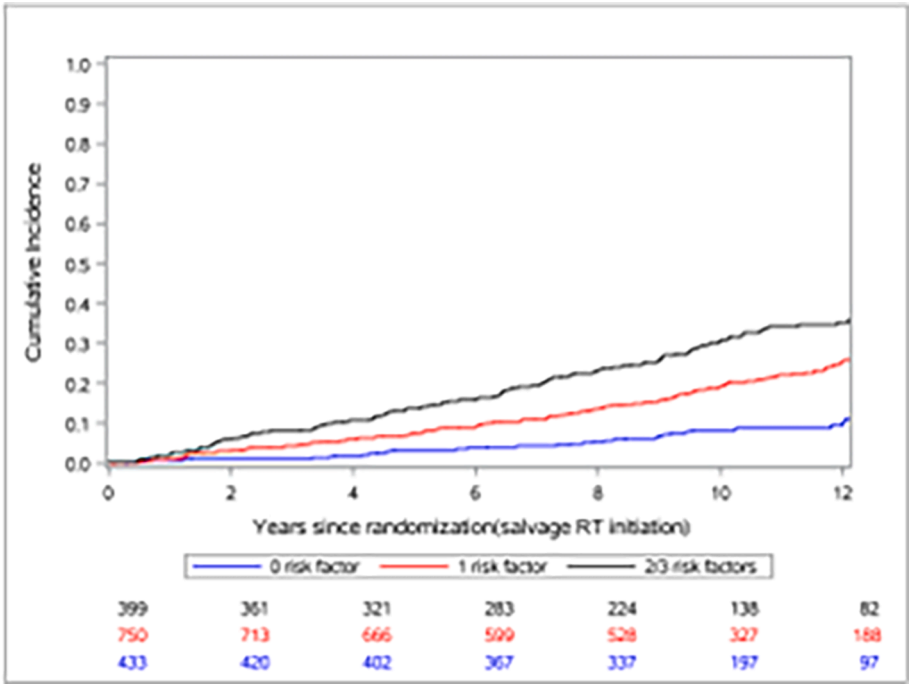

Fig. 3A. Cumulative incidences of clinical progression according to number of risk factors (GS 8-10, PSA at SRT start >0.5 ng/mL and negative margin) in overall population.

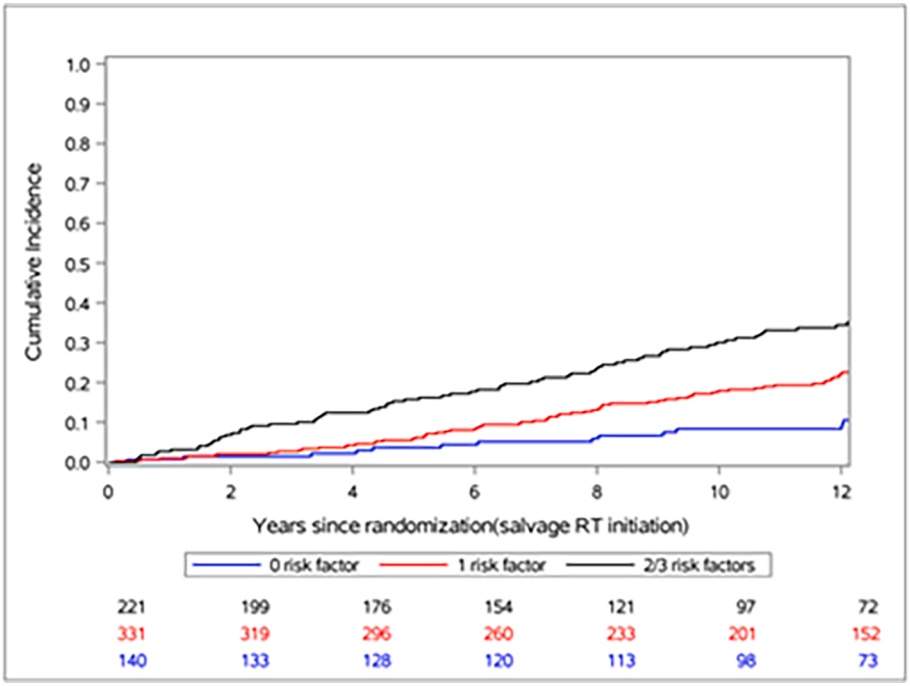

Fig. 3B. Cumulative incidences of clinical progression according to number of risk factors (GS 8-10, PSA at SRT start >0.5 ng/mL and negative margin) in patients with persistent PSA post RP.

randomization but from a subset of patients who received delayed SRT. Although the data for this IPD meta-analysis were prospectively collected and the quality of the data were considered relevant for this study, we cannot perform a reliable comparative analysis between the treatment arms (SRT alone or associated with HT, either LHRH agonist or bicalutamide or duration of HT) due to small numbers of patients with a GS $\geq$ 8 and lack of randomization of HT modalities. RT field and radiation dose data were only available in a subset of patients from the GETUG16 trial. Therefore, we could not include these variables in the multivariable models or subgroup analyses. Biochemical PFS is not readily available as each trial uses a different definition for BCR. Subsequent treatment at recurrence to SRT is available for GETUG16, and RTOG9601, but not for EORTC22911.

In addition, there have been substantial changes in Gleason grading, imaging, and radiotherapy dose, fields and technique that likely impact the absolute event rates in contemporary cohorts. Notably, PSMA-PET based RT planning may lead to better outcomes compared to conventional imaging [15] but studies are needed to define whether and how

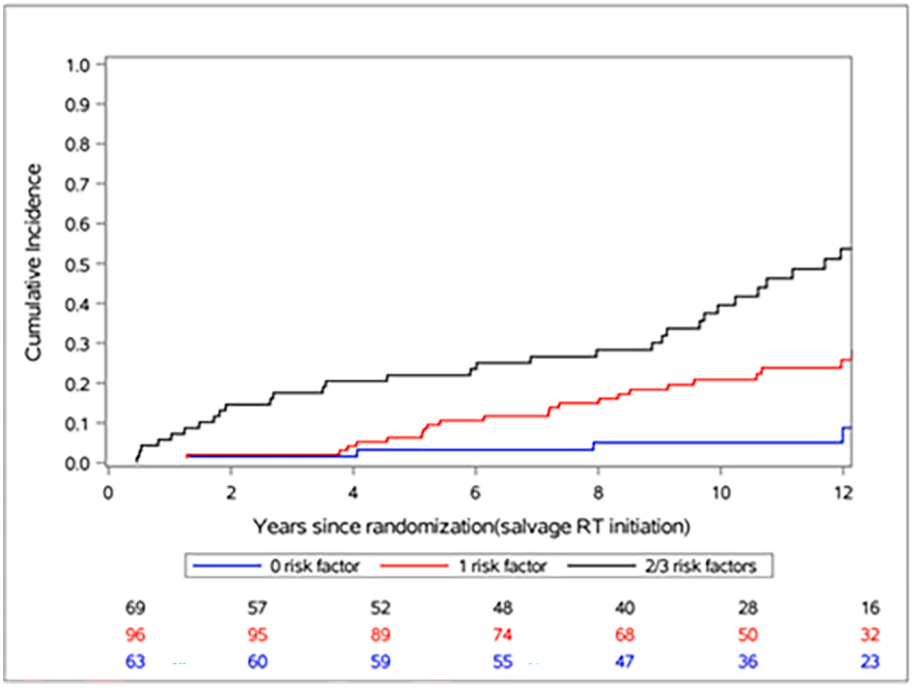

Fig. 3C. Cumulative incidences of clinical progression according to number of risk factors (GS 8-10, PSA at SRT start >0.5 ng/mL and negative margin) in patients initiating SRT within 1-year post RP.

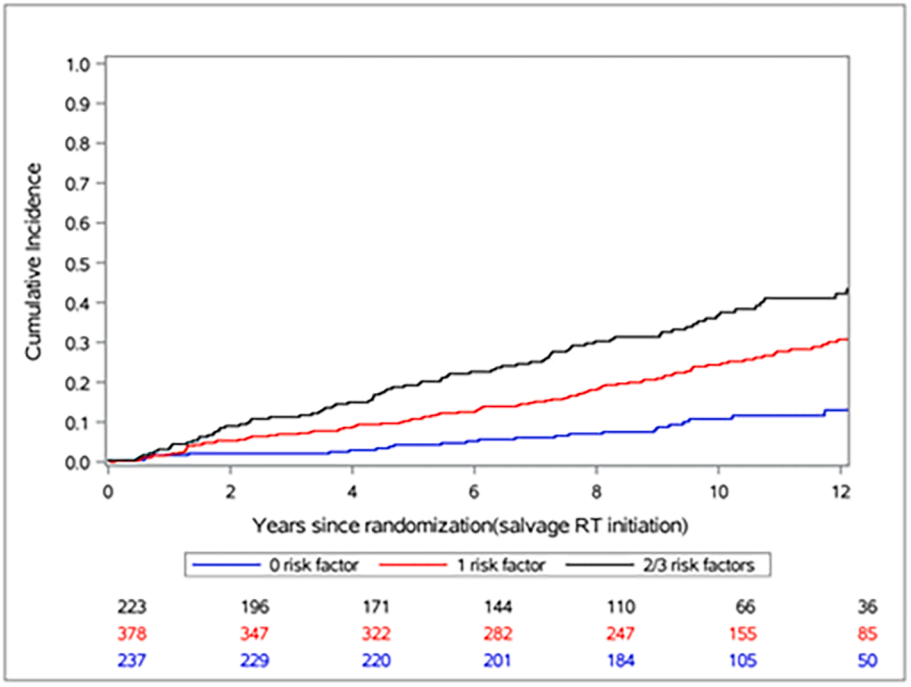

Fig. 3D. Cumulative incidences of clinical progression according to number of risk factors (GS 8-10, PSA at SRT start >0.5 ng/mL and negative margin) in patients receiving SRT alone.

PSMA-PET-CT imaging can improve outcomes. New approaches, especially genomic markers [16] or artificial intelligence for histopathology analysis [17] have proven to provide a prognostic information in patients with prostate cancer treated with primary radiotherapy (+/−HT) and may also help further identify men who candidates for treatment intensification of systemic therapy in SRT setting.

A notable strength of this paper is ability to report 10-year outcomes which is relevant for patients who are chosen for prostatectomy as routine care. Namely, a significant portion of the men will live many years after the prostatectomy and are at risk for a relapse and treatment for many years with hormonal therapy for a second relapse and die from a non-prostate cause. Moreover, the impact of death from other causes may explain why a treatment may have a significant impact on time to clinical progression, time to distant metastases and MFS but not OS. As such treatment intensification to prevent a second PSA relapse with goal of preventing long term hormonal therapy and/or metastatic event may be beneficial.

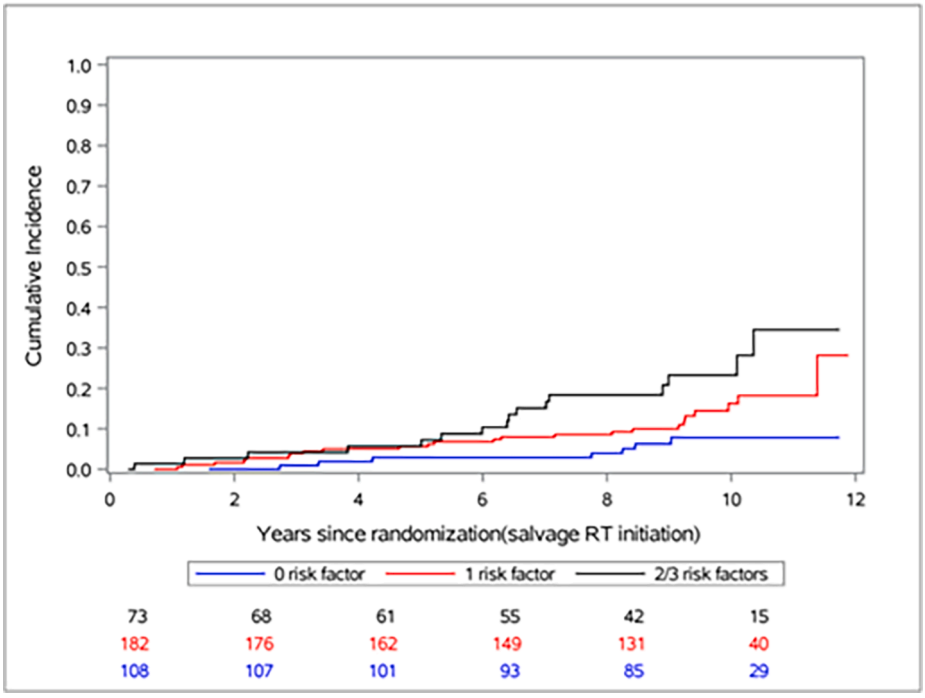

Fig. 3E. Cumulative incidences of clinical progression according to number of risk factors (GS 8-10, PSA at SRT start >0.5 ng/mL and negative margin) in patients receiving SRT + 6-month LHRH agonist.

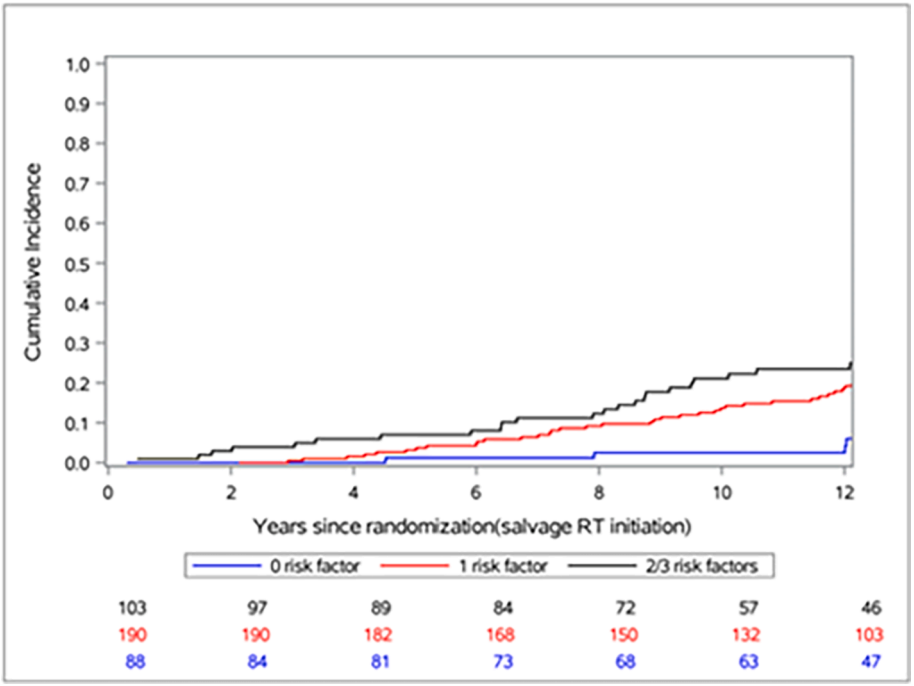

Fig. 3F. Cumulative incidences of clinical progression according to number of risk factors (GS 8-10, PSA at SRT start >0.5 ng/mL and negative margin) in patients receiving SRT + 24 months Bicalutamide.

Conclusion

Patients treated with SRT post prostatectomy have heterogeneous outcomes. GS $\geq$ 8, PSA at SRT of $\geq$0.5 at time of SRT and margin status were the strongest prognostic variables across the endpoints. Using these variables, we derived a simple clinic-pathological risk scoring system of 0 versus 1 versus 2/3 RF which details distinct high, intermediate and low risk groups both with or without HT. These data provide prognostic information for individual patient counselling as well as guidance for interpretation of completed and ongoing trials and design of future clinical trials in the salvage setting.

CRediT authorship contribution statement

Pascal Pommier: Writing – original draft, Validation, Supervision, Investigation, Conceptualization. **Wanling Xie:** Writing – original draft,

Validation, Supervision, Formal analysis, Conceptualization. **Praful Ravi:** Writing – original draft, Validation, Conceptualization. **Christian Carrie:** Validation. **James J. Dignam:** Validation. **Felix Feng:** Validation. **Paul Sargos:** Validation. **Silke Gillessen Sommer:** Validation. **Daniel E. Spratt:** Validation. **Bertrand Tombal:** Validation. **Hendrik Van Poppel:** Validation. **Christopher Sweeney:** Writing – original draft, Validation, Supervision, Investigation, Conceptualization.

Declaration of competing interest

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

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110532.

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