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Predictors and rate of adjuvant radiation therapy following radical prostatectomy: A report from the Prostate Cancer Registry

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Abstract

Introduction: Long-term data from three randomized trials have demonstrated that adjuvant radiation therapy (ART) reduces the rate of biochemical failure in high-risk men following radical prostatectomy (RP). One of these trials has shown a survival advantage. We investigated the rate of ART in Victoria and the predictors for this treatment.
Methods: We analysed data from eligible patients who were notified to the Victorian Prostate Cancer Registry (PCR) by 37 Victorian hospitals between 1 August 2008 and 31 October 2011. We defined ART as radiation therapy (RT) delivered within 6 months of RP. Predictors of ART receipt were modelled using adjusted and unadjusted logistic regression.
Results: There were 4626 eligible cases from which 2018 underwent RP with recorded date of surgery. Of these eligible prostatectomy cases, a total of 89 received ART. A subgroup of 833 men had an adverse pathologic feature, of whom 78 received ART. In a multivariate model, pathologic tumour stage pT3a (odds ratio (OR) 2.64; 95% confidence interval (CI) 1.4–5.00; $P = 0.003$), pT3b (OR 4.58; 95% CI 2.12–9.89; $P = 0.000$), a positive surgical margin (OR 8.91; 95% CI 4.61–17.2; $P = 0.000$) and pathologic Gleason grade >7 (OR 7.18; 95% CI 1.54–33.6; $P = 0.012$) predicted receipt of ART.
Conclusion: Adverse pathologic features and high pathologic Gleason score predict for receiving ART in Victorian men after RP, but overall, ART is not commonly prescribed. This finding is consistent with other published series and may reflect clinician scepticism regarding the benefit of ART over salvage RT and concern about toxicity and the risk of over treatment.

Key words: adjuvant; Gleason score; prostatectomy; prostatic neoplasm; radiotherapy.

Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous cancer in men, by 2010 accounting for over 30% of new notifiable cancer diagnoses in Australian men.[1] Men in Australia are now more likely to be diagnosed at an early stage,[2] affording them the option of curative treatments such as radical prostatectomy (RP) or radiation therapy (RT). Following RP, significant numbers of men will suffer local recurrence. These men will have a high risk of developing metastatic disease from which they may eventually succumb.[3]

External beam radiation treatment has been administered as 'salvage' RT (SRT) for men with local recurrence following RP, with an apparent positive long-term effect on disease control.[4] The proposal that RT might therefore be useful to administer in the adjuvant, or immediate postoperative, setting for those men at high risk of recurrence after RP, stimulated the design of three prospective randomized controlled trials (South-

west Oncology Group trial 8794 (SWOG 8794), 1988–1997; European Organization for Research and Treatment of Cancer trial 22911 (EORTC 22911), 1992–2001; and the German ARO 96-02 trial, 1997–2004), to test this hypothesis. In recent years, long-term follow-up from each of these trials has demonstrated that adjuvant RT (ART) improves disease control in men with high-risk pathologic findings.[5–8] SWOG 8794, with the longest follow-up, also reported improved overall survival.[5] This evidence has led to recommendations in evidence-based guidelines for consideration of immediate postoperative treatment in men at high risk after RP.[9–11] Despite these recommendations, published rates of ART prescription in American series are low.[12,13] We examined data from the Victorian Prostate Cancer Registry (PCR)[14] to identify the rate of ART in Victorian men and the factors which predict for this treatment.

Methods

Data collection and definitions

Records of prostatectomy cases were obtained from the PCR, established in 2009 initially in four hospitals (accounting for 25% of all notifications to the Victorian Cancer Registry) to assess patterns of presentation, care and outcomes. By 2011, an additional 34 hospitals had joined, resulting in the registry accruing approximately 75% of new Victorian prostate cancer cases. Registry recruitment is linked with mandatory notification of cancer status to the population-based Victorian Cancer Registry. Details of the recruitment strategy have been described previously.[14]

Data are collected by medical record review and through a follow up interview of men and record of available prostate-specific antigen (PSA) levels at 12 and 24 months post diagnosis. Men with a biopsy-confirmed diagnosis of prostate cancer and who underwent RP were eligible for inclusion in this study. All men have had at least 12 months follow up, but some have had longer based on their date of diagnosis. Those men who underwent RP, but did not have a date of surgery recorded were excluded. Figure 1 details the recruitment of cases for inclusion in this study.

The consistent registry collection of PSA levels was restricted to specific time points; we did not have reliable data on interval levels of PSA, and we could not make inferences about the clinician's intent for the immediate postoperative RT and whether it might have been recommended on the basis of a detectable PSA. We discriminated, therefore, between radiation given 'immediately' postoperative as an 'adjunct' or 'adjuvant' to the surgery, and radiation given at later time points. Our operational definition of ART is 'RT commenced within 6 months of RP'.

We determined whether a diagnosing institute was metropolitan or regional on the basis of postcode. The included surgical approaches were open surgery, laparoscopic surgery, robot-assisted surgery and conversion to open surgery. Men with pT3a and pT3 (not otherwise specified) tumour stage were combined into a 'real pT3a' tumour category (in concordance with 'general rule 4' of the TNM staging system). A positive surgical margin (PSM) refers to the presence of any extent of tumour at any surgical margin. On-site RT describes surgical centres that also have RT facilities on the same site.

Ethical approval was gained from participating hospitals, Monash University and the Cancer Council Victoria.

Statistical analyses

Categorical variables were summarized using frequency and percentage. Continuous variables were assessed for significant departures from normality using a Shapiro–Wilk test and summarized using mean and standard deviation (SD) or median and inter-quartile range as appropriate. Predictors of RT within 6 months of RP were investigated using unadjusted and adjusted logistic regression. A logistic approach was favoured because of the comparative rarity of the outcome variable: only 89 (4.4%) of the overall sample of 2018 men received postoperative RT within 6 months. Candidate predictors for inclusion in the adjusted model were selected on the basis of performance on unadjusted modelling in addition to considerations of clinically important covariates. Interactions between pairs of concurrent adjusted model predictors were tested for. Overall fit of the model was assessed using a Hosmer–Lemeshow goodness of fit test. All reported P values are two-tailed and for each analysis $P < 0.05$ was considered significant. All analyses were performed using Stata version 12 (StataCorp, College Station, TX, USA).

Results

A total of 2018 men underwent RP for prostate cancer and were eligible for analysis, 89 of whom received ART according to our definition (Table 1). Of these 2018 men, 649 (32%) had pathologic evidence of extracapsular extension or seminal vesicle invasion (pT3a or pT3b) and 557 (28%) had positive surgical margins. Seventy-one of 557 men (12.7%) with PSM received ART, while 40 of 506 men (7.9%) with stage pT3a disease and 26 of 143 men (18.2%) with stage pT3b disease received ART. An 'adverse pathologic features' subgroup (comprising 833 men (41%) with at least one adverse pathologic feature (any of PSM, pT3a, or pT3b) and no evidence of lymph node metastases) had 78 men (9.4%) who received ART. Eleven men received ART despite not having an adverse pathologic feature.

The presence of an adverse pathologic feature was associated with a significantly increased likelihood of receiving ART in a multivariate model (Table 2); PSM (odds ratio (OR) 8.91; 95% confidence interval (CI)

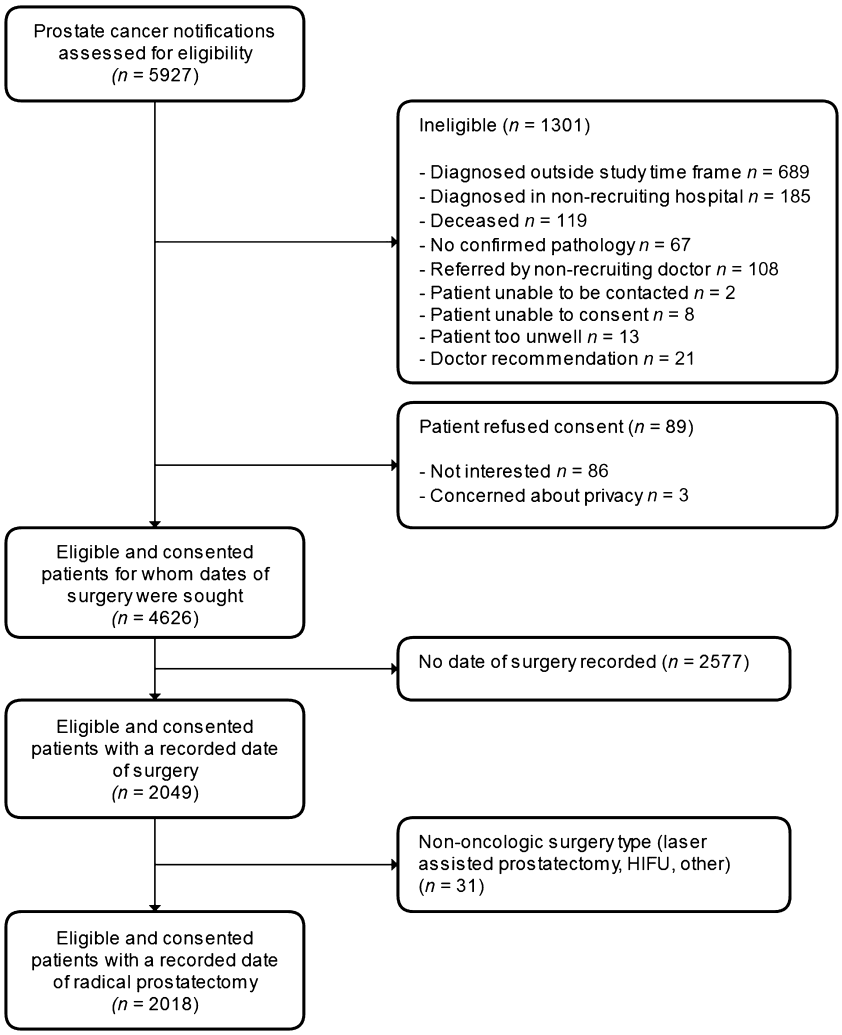

Fig. 1. Recruitment of cases for inclusion in the study.

4.61–17.2; $P = 0.000$), stage pT3a (OR 2.64; 95% CI 1.40–5.00; $P = 0.003$) or stage pT3b disease (OR 4.58; 95% CI 2.12–9.89; $P = 0.000$). Only five men had pT4 disease, and only one of these underwent ART. Pathologic confirmation of pelvic lymph node metastases was not associated with any significant effect on receipt of ART and in more than half of the subjects a pelvic lymph node dissection was not performed (pNx). High pathologic tumour grade (Gleason > 7) was also associated with a significantly increased likelihood of ART prescription (OR 7.18; 95% CI 1.53–33.6; $P = 0.012$).

Of the demographic and treatment factors that were tested in a multivariate model, men undergoing robotic surgery were less likely to receive ART than those who had an open RP (OR 0.421; 95% CI 0.211–0.841; $P = 0.014$), and men undergoing RP at a private hospital were less likely to receive ART than those treated at a public facility (OR 0.513; 95% CI 0.274–0.960; $P = 0.037$). A diagnosis of prostate cancer in a non-metropolitan centre did not significantly affect the chance of receiving ART. Similarly, age at diagnosis or the availability of on-site RT facilities did not affect the likelihood of receiving ART.

When the multivariate analysis was limited to men with an adverse pathologic feature (Table 3), the association of lower rates of ART with robotic surgical approach (OR 0.480; 95% CI 0.231–0.997; $P = 0.049$) persisted, but association of lower rates of ART with treatment at a private centre (OR 0.525; 95% CI 0.265–1.04; $P = 0.064$) and with pathologic Gleason grade did not (OR 4.55; 95% CI 0.928–22.3; $P = 0.062$).

Discussion

We have used the PCR to investigate the use of ART after RP in Victorian men. Our data show surgical outcomes (PSM rate 27.6%) and distribution of prostate cancer stages (pT3a 25.1%, pT3b 7.09%) that are consistent

Table 1. Characteristics of patient cohort

Characteristic	Level	Postoperative radiation therapy within 6 months	
		Yes (*n* = 89)	No (*n* = 1929)
Age at diagnosis	Mean (SD)	62.1 (6.9)	61.9 (6.8)
	Median (IQR)	63.2 (56.2, 67.5)	62.6 (57.4, 66.9)
Diagnosis institute	Metro	76 (85.4)	1510 (78.3)
n (col %)	Regional	8 (9.0)	281 (14.6)
	Not stated	5 (5.6)	138 (7.2)
Surgery institute	Public	39 (43.8)	422 (21.9)
n (col %)	Private	49 (55.1)	1493 (77.4)
	Not stated	1 (1.1)	14 (0.7)
Surgical approach	Open	71 (79.8)	1074 (55.7)
n (col %)	Laparoscopic	4 (4.5)	160 (8.3)
	Robot	14 (15.7)	695 (36.0)
On-site radiation	Yes	37 (41.6)	672 (34.8)
n (col %)	No	52 (58.4)	1257 (65.2)
Initial PSA (ng/mL)	≤ 4	8 (9.0)	339 (17.6)
n (col %)	4.1–10	57 (64.0)	1295 (67.1)
	10.1–20	16 (18.0)	211 (10.9)
	>20	7 (7.9)	68 (3.5)
	Not stated	1 (1.1)	16 (0.8)
pT	pT2	17 (19.1)	1197 (62.1)
n (col %)	pT3a	40 (44.9)	466 (24.2)
	pT3b	26 (29.2)	117 (6.1)
	pT4	1 (1.1)	4 (0.2)
	Other	4 (4.5)	129 (6.7)
	Not stated	1 (1.12)	16 (0.8)
pN	pN0	55 (61.8)	800 (41.5)
n (col %)	pN1	3 (3.4)	39 (2.0)
	pNX	31 (34.8)	1073 (55.6)
	Not stated	0 (0.0)	17 (0.9)
Positive margin	No	13 (14.6)	1378 (71.4)
n (col %)	Yes	71 (79.8)	486 (25.2)
	Equivocal	2 (2.25)	39 (2.0)
	Not stated	3 (3.4)	26 (1.4)
Pathologic Gleason	<7	2 (2.25)	285 (14.8)
n (col %)	3 + 4	22 (24.7)	975 (50.5)
	4 + 3	33 (37.1)	459 (23.8)
	>7	28 (31.5)	174 (9.0)
	Not stated	4 (4.5)	36 (1.9)

IQR, inter-quartile range; PSA, prostate-specific antigen; SD, standard deviation.

with other published series.[15] It is apparent that the rate of ART prescription is lower than the rate of adverse pathologic features – only 9.4% of such men in the PCR received this treatment. Evidence from the Surveillance, Epidemiology and End Results program (SEER) suggests that rates of ART in the United States are similarly low, with no increase in prescriptions following the publication in 2006 of the 10 year SWOG 8794 results.[12,13]

The low rate of ART might be explained by several factors. Firstly, critics of these trials have observed that the trial designs did not compare adjuvant RT with early salvage RT; the lack of a clear protocol for the observation arms in SWOG 8794 and EORTC 22911 meant that some men did not receive salvage RT at all, or they received it late enough to be of doubtful benefit.[16] Furthermore, only the recent ARO 96-02 trial specified undetectable PSA following RP, and so it could be argued that the earlier trials did not distinguish between truly 'adjuvant' and early salvage RT.[16] A second focus of criticism is whether tangible clinical benefits (e.g. overall survival, freedom from clinical recurrence) can be extrapolated from improved time to PSA recurrence. The long-term follow-up of EORTC 22911 at 10.6 years found that the gains conferred by ART in biochemical progression-free survival and local control in the interim analysis were maintained, but the improvement in recurrence-free survival did not persist.[6] Longer-term follow up of SWOG 8794 *has* reported an improved overall survival in the ART arm, but this result is controversial because of the possible influence of comorbid illness on the low survival in the control group.[5,17]

Secondly, there is concern that ART for men with adverse pathologic features constitutes overtreatment and unnecessary exposure to the risk of further toxicity. Genitourinary and rectal complications are more commonly observed with ART but it appears that the effect is small and may not negatively affect quality of life.[8,18–20] Significantly, the most recent trial (ARO 96-02) also reported a lower overall rate of RT complications than either of the earlier trials; a small increase in late Grade 2 GU (2% vs. 0%) and GI (1% vs. 0%) toxicity with ART and only one instance of Grade 3 toxicity,[7] perhaps attributable in part to the use of the more modern three-dimensional conformal radiation therapy technique.[7,21] Intensity-modulated radiation therapy is now commonly used in prostate RT and still further reductions in late GI toxicity may be possible with the use of this technique.[22]

Thirdly, there is the hypothesis that the early delivery of SRT might be equivalent to ART in some high-risk men.[4,23,24] Evidence from a systematic review of SRT series using a tumour control probability model suggests that prescription of SRT at the earliest detectable PSA titre gives the greatest likelihood of freedom from biochemical failure.[25] The author of that study concludes that initiation of early SRT at very low levels of detectable PSA may offer the same benefit as ART. Nevertheless, the appropriate threshold for delivery of salvage treatment has not been defined. Clinical trials that directly compare adjuvant RT with early salvage RT are currently recruiting patients.[26–28]

Finally, there is evidence that the initial therapy chosen by a patient for their prostate cancer is highly correlated with the specialty that was first consulted for the condition.[29,30] Two American surveys of physician attitudes to ART prescription have found that significantly fewer urologists than radiation oncologists would prescribe ART on the basis of adverse pathologic features alone (78% of radiation oncologists vs. 44% of urologists in one series).[31,32] If these results are applicable to Australian practice, then a low early referral rate

Table 2. Multivariate logistic regression model for predictors of ART in entire sample

Predictor variable	Level	Adjusted OR	SE	*z*	*P* > z	(95% CI)	
Age at diagnosis	–	0.978	0.018	–1.210	0.228	0.943	1.014
Diagnosis institute location	Metro	1.0					
	Regional	0.579	0.252	–1.260	0.209	0.247	1.357
Surgery institute	Public	1.0					
	Private	0.513	0.164	–2.090	0.037	0.274	0.960
Surgical approach	Open	1.0					
	Laparoscopic	0.386	0.218	–1.690	0.092	0.128	1.167
	Robotic	0.421	0.149	–2.450	0.014	0.211	0.841
On-site radiation	No	1.0					
	Yes	0.901	0.287	–0.330	0.744	0.483	1.681
Initial PSA (ng/mL)	≤ 4	1.0					
	4.1–10.0	1.111	0.468	0.250	0.804	0.486	2.539
	10.1–20.0	1.026	0.515	0.050	0.959	0.384	2.744
	>20	0.632	0.382	–0.760	0.448	0.193	2.066
pT	T2	1.0					
	T3a	2.639	0.859	2.980	0.003	1.395	4.995
	T3b	4.580	1.799	3.880	0.000	2.122	9.889
	T4	16.335	23.335	1.960	0.051	0.994	268.572
pN	pN0	1.0					
	pN1	0.292	0.196	–1.840	0.066	0.078	1.086
	pNX	0.787	0.215	–0.880	0.380	0.461	1.343
Positive margin	No	1.0					
	Yes	8.912	2.996	6.510	0.000	4.612	17.222
Pathologic Gleason	<7	1.0					
	3 + 4	1.709	1.307	0.700	0.483	0.382	7.653
	4 + 3	3.357	2.588	1.570	0.116	0.740	15.215
	>7	7.181	5.654	2.500	0.012	1.535	33.600

CI, confidence interval; OR, odds ratio; SE, standard error.

to radiation oncologists for discussion of ART in the event of adverse pathologic features may contribute to the low rate of ART in high-risk men.

Our data have shown that adverse pathologic features (pT3a, pT3b, PSM) and high pathologic Gleason grade predict for receipt of ART in Victoria. That three of the four predictors for ART in our data are the indications listed in published guidelines[9–11] suggests that, when it is prescribed, ART is generally prescribed for appropriate indications. We had thought that in limiting the analysis to only those men with adverse pathologic features that the influence of non-evidence-based factors on ART prescription such as on-site availability, high Gleason grade and patient age may have become more apparent. In the SEER data, men with Gleason 8–10 disease were more likely to be referred for ART (a finding which we observed in our entire sample, but not to a significant level in the subgroup of men adverse pathologic features), as were younger men (which we did not observe in our data).[12] It may be that the low event rate made detection of these predictors difficult, it is also possible that stronger indications (such as detectable post-op PSA) that we did not test for exerted a greater independent effect than our tested variables. Recently published data from the PCR has shown that robotic RP is associated with a lower rate of PSM than other surgical approaches.[33] In our multivariate model robotic RP (and surgery at a private centre) were associated with a lower likelihood of receiving ART, independent of margin status. This may reflect the practice of private institutions, and those equipped with robotic surgical facilities, or may be a chance finding.

The PCR captures approximately 75% of all Victorian prostate cancer diagnoses and includes providers from the public and private health care system in rural and metropolitan areas.[2] The locations from which the registry does not currently capture diagnoses do not outwardly appear systematically different in characteristics from those from which we do capture data, and we have 98% ascertainment from the included locations. We believe our results can thus be generalised to the state population, but as this report is a retrospective analysis of data from a disease registry, it is possible that individual patient and clinician characteristics for which we could not control may have influenced treatment decisions and this may have influenced our results.

There are other limitations that must be considered when interpreting these findings. Our operational definition of ART includes all RT administered within 6 months of RP. This cut-off was chosen to capture as many true 'adjuvant' RT prescriptions (based on adverse pathologic features) while excluding salvage RT prescribed for

Table 3. Multivariate logistic regression model for predictors of ART in men with adverse pathologic features

Predictor variable	Level	Adjusted OR	SE	*z*	*P* > z	(95% CI)	
Age at diagnosis	–	0.973	0.019	–1.420	0.155	0.936	1.011
Diagnosis institute location	Metro	1					
	Regional	0.449	0.230	–1.560	0.118	0.165	1.224
Surgery institute	Public	1					
	Private	0.525	0.183	–1.850	0.064	0.265	1.039
Surgical approach	Open	1					
	Laparoscopic	0.345	0.225	–1.630	0.103	0.096	1.241
	Robotic	0.480	0.179	–1.970	0.049	0.231	0.997
On-site radiation	No	1					
	Yes	0.829	0.288	–0.540	0.589	0.420	1.637
Initial PSA	≤ 4	1					
	4.1–10	0.973	0.445	–0.060	0.953	0.397	2.385
	10.1–20	0.783	0.427	–0.450	0.654	0.269	2.282
	>20	0.547	0.348	–0.950	0.343	0.157	1.906
pT	T2	1					
	T3a	2.372	0.893	2.290	0.022	1.134	4.961
	T3b	4.368	1.901	3.390	0.001	1.861	10.252
	T4	–					
pN	pN0	1					
	pNX	0.681	0.197	–1.320	0.185	0.386	1.202
Positive margin	No	1					
	Yes	7.319	3.109	4.690	0.000	3.183	16.829
Pathologic Gleason	<7	1					
	3 + 4	1.136	0.892	0.160	0.871	0.244	5.297
	4 + 3	1.987	1.580	0.860	0.388	0.418	9.444
	>7	4.553	3.695	1.870	0.062	0.928	22.344

CI, confidence interval; OR, odds ratio; SE, standard error.

detectable and/or rising PSA. It is also the current definition of the upper time limit for commencement of ART prescription in the Radiotherapy – Adjuvant Versus Early Salvage (RAVES) randomised trial of the timing of postoperative RT.[26] Whether a detectable postoperative PSA level exerted an independent effect on postoperative RT prescription could not be tested because PSA level is not reliably recorded in the PCR for this time point. It is possible that men with detectable post-op PSA were referred for early salvage RT within 6 months of RP and this uncertainty means that our results might overestimate the rate of ART prescription. It is also possible that some men received 'adjuvant' intent RT for adverse pathologic features later than 6 months after RP. As the PCR records only the receipt of RT, we cannot comment on the number of men who were offered ART, but declined it. RT body site or dose are not recorded in the PCR, which means that it is possible, but unlikely within 6 months of RP, that we have included men receiving RT to sites other than the prostate bed. We are also unable to comment on whether radiation doses were consistent with published guidelines.[9–11]

Conclusion

Victorian men with adverse pathological features following RP comprise the majority of ART recipients, but the overall rate of ART prescription in this group is low. This is despite multiple evidence-based guidelines recommending consideration of ART for men with high-risk disease after RP, as high level evidence is that adjuvant RT is a well-tolerated treatment significantly improving biochemical recurrence-free survival and, in the study with the longest follow up, improving overall survival. We can only speculate why this might be, but scepticism regarding the available trial data, concern about overtreatment and lack of discussion of this treatment option may all be contributory.

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