Comparison of salvage radical prostatectomy vs. salvage ablation therapy for biopsy-proven radio-recurrent localized prostate cancer

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ABSTRACT

INTRODUCTION: Radiation therapy for prostate cancer is associated with a 15–20% five-year recurrence rate. Patients with recurrence in the prostate only are candidates for salvage local therapies; however, there is no consensus on modality. This study uses registries at Memorial Sloan Kettering Cancer Center (MSKCC) and University of Western Ontario (UWO) to compare the oncologic outcomes of salvage radical prostatectomy (SRP) and salvage ablation (SA).

METHODS: A total of 444 patients were available for analysis. Due to intergroup differences, propensity score methodology was used and identified 378 patients with more comparable pre-salvage prostate-specific antigen (PSA), Gleason score, and primary radiation treatment. Patients underwent SRP at MSKCC and SA at UWO.

RESULTS: Of the 378 patients, 48 died of disease, with a 6.0-year median (interquartile range [IQR] 3.0, 9.7) followup among survivors; 88 developed metastases, with a median 4.6-year (IQR 2.3, 7.9) followup among metastasis-free survivors. There was a non-significantly higher rate of cancer-specific (hazard ratio [HR] 1.02, 95% confidence interval [CI] 0.51, 2.06, p=0.9) and improved metastasis-free survival (HR 0.71, 95% CI 0.44, 1.13, p=0.15) among patients undergoing SA compared to patients undergoing SRP. There were 143 patients who received hormonal therapy, with higher rates of androgen deprivation therapy (ADT) in SA (HR 1.42, 95% CI 0.97, 2.08, p=0.068), although this did not meet conventional levels of significance.

CONCLUSIONS: This propensity score analysis of salvage therapy for radio-recurrent prostate cancer identified no statistically significant differences in oncologic outcome between SRP and SA; however, there was evidence of a lower risk of ADT in the cohort undergoing SRP. Given they are both potentially curative therapies, these treatments are viable options for men with clinically localized, radio-recurrent prostate cancer rather than ADT alone. Future research may further elucidate subpopulations that may be more amenable to either SRP or SA.

INTRODUCTION

Therapy for localized prostate cancer includes two major modalities: radiation therapy or radical prostatectomy. With contemporary external beam radiation therapy (EBRT) using 78–79.2 Gy, the approximate five-year biochemical recurrence-free survival is 80–85%,[1,2] and historic figures indicates that localized failures occur in 13–35% at 10 years.[3] Given this 15–20% recurrence rate, there is a need for salvage therapies for patients who develop recurrence.

Patients with biopsy and imaging-proven localized prostate cancer recurrence are candidates for local salvage therapies, including salvage radical prostatectomy (SRP),[4] salvage radiotherapy,[5] and salvage ablative therapies, such as cryotherapy[6,7] and high-intensity focused ultrasound (HIFU).[8-11]

Despite the efficacy of salvage local therapies,[4-6,8,12,13] many urologists treat these patients with androgen deprivation therapy (ADT) alone due to concerns regarding therapeutic benefit and potential for complications with techniques. ADT, however, is non-curative and exposes the patient to the potential risks of ADT, including cardiovascular toxicity.[14]

SRP is a technically challenging surgical procedure, with a risk for significant surgical complications.[9,12] This has led to the evaluation of alternative treatment strategies by our group and others, including HIFU[8] and cryotherapy.[6] These minimally invasive ablative alternatives are less technically challenging

KEY MESSAGES

- Both salvage ablation (SA) and salvage radical prostatectomy are viable options for salvage therapy for radio-recurrent prostate cancer, achieving approximately 85% CSS and 65–70% metastasis-free survival at 9 years.
- In this propensity-matched, retrospective cohort comparison, there was no significant difference in CSS and MFS, while there was a trend towards higher rates of ADT in the SA group.
- Clinicians should strongly consider local salvage therapy for radio-recurrent prostate cancer.

than SRP, although there is the possibility of incomplete elimination of the cancer and their own morbidity profiles.[5,9,13] Given the ongoing lack of clear consensus with regards to local salvage modality preference, we compared oncologic outcomes after SRP to patients treated with salvage ablation (SA) in radio-recurrent prostate cancer.

METHODS

Data from two independently maintained registries were retrospectively analyzed. All patients undergoing SRP were treated at Memorial Sloan Kettering Cancer Center (MSKCC), and all patients undergoing salvage ablation were patients treated at the University of Western Ontario (UWO). Patients undergoing salvage cryoablation were treated between 1995 and 2004, SRP were treated between 2000 and 2015, and salvage HIFU were treated between 2006 and 2015.

Cryoablation and HIFU are both minimally invasive ablative treatments that use different targeting and treatment mechanisms. Since it is unclear whether it is more appropriate to combine these two treatment options as one group or to keep them as separate groups, we compared these two modalities for the outcome of metastasis-free survival (MFS) to make this decision. Since we saw no evidence of a difference between cryoablation and HIFU (MFS hazard ratio [HR] for HIFU, with cryoablation as the reference group: 1.49; 95% confidence interval [CI] 0.75, 2.96, p=0.3), comparisons between treatment types were between SA (combined cryoablation or HIFU) and SRP.

We identified 519 patients who underwent primary radiotherapy treatment for their prostate cancer, who then went on to undergo salvage cryoablation, HIFU, or SRP. We excluded 15 patients with unknown pre-salvage prostate-specific antigen (PSA), 54 patients with unknown pre-salvage Gleason score, and six patients with unknown time to death or metastasis, leaving us with a cohort of 444 men for analysis.

As there were noticeable differences between treatment groups, we used propensity score methodology to identify patients for whom comparison between treatments is not appropriate, on the grounds that they had an extremely high probability of being treated by one or the other treatment. Propensity scores were also used to adjust for differences between groups.

We first created a multivariable logistic model to calculate the propensity score as the probability of undergoing SA using pre-salvage PSA, pre-salvage Gleason score, and primary radiation treatment. We excluded 66 (26 SRP and 40 SA) patients with scores at the extremes (probability <0.05 or >0.85, where, of note, there were no patients who underwent SRP and had a propensity score >0.90) for a more balanced cohort. Figure 1 shows the distribution of the propensity scores based on treatment groups.

We then used multivariable Cox proportional hazard regression models, adjusting for the propensity score, to assess the association between treatment type and MFS and cancer-specific survival (CSS) separately. We were additionally interested in the rate of hormone use after primary salvage treatment, as this adversely affects a patient's quality of life. All statistical analyses were conducted using STATA 15.0 (StataCorp, College Station, TX, U.S.).

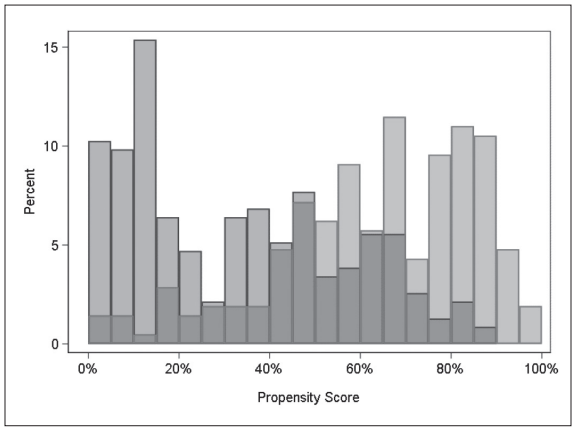

Figure 1. Histogram of propensity score for patients available for analysis who underwent salvage radical prostatectomy (light gray) and salvage ablation (dark gray) (N=444).

Table 1. Patient and disease characteristic based on salvage treatment

	Cohort of patients available for analysis (n=444)			Final cohort in analysis (n=378)		
	Radical prostatectomy (n=234; 53%)	Ablation (n=210; 47%)	p*	Radical prostatectomy (n=208; 55%)	Ablation (n=170; 45%)	p*
Primary radiation treatment			<0.0001			<0.0001
External beam	133 (57%)	194 (92%)		131 (63%)	158 (93%)	
Brachytherapy	74 (32%)	12 (5.7%)		59 (28%)	10 (5.9%)	
Combination of brachytherapy and external beam	6 (2.6%)	1 (0.5%)		5 (2.4%)	1 (0.6%)	
Other	21 (9.0%)	2 (1.0%)		13 (6.3%)	1 (0.6%)	
Unknown	0 (0%)	1 (0.5%)		0 (0%)	0 (0%)	
Age at salvage treatment	65 (60, 69)	71 (66, 74)	<0.0001	66 (62, 69)	69 (65, 73)	<0.0001
Hormonal treatment prior to salvage treatment	77 (33%)	89 (42%)	0.0001	71 (34%)	70 (41%)	0.2
Unknown	0 (0%)	39 (19%)		0 (0%)	28 (16%)	
PSA prior to salvage treatment	3.7 (1.9, 6.3)	4.5 (2.8, 7.4)	0.004	4.1 (2.0, 6.4)	4.5 (2.7, 6.7)	0.089
Gleason grade prior to salvage treatment (categorized)			0.0001			0.3
≤6	26 (11%)	54 (26%)		24 (12%)	24 (14%)	
7	125 (53%)	82 (39%)		110 (53%)	76 (45%)	
≥8	83 (35%)	74 (35%)		74 (36%)	70 (41%)	
Year of salvage treatment			<0.0001			<0.0001
1995–1999	0 (0%)	75 (36%)		0 (0%)	56 (33%)	
2000–2004	45 (19%)	72 (34%)		37 (18%)	58 (34%)	
2005–2009	104 (44%)	44 (21%)		95 (46%)	41 (24%)	
2010–2015	85 (36%)	19 (9.0%)		76 (37%)	15 (8.8%)	

All results are median (IQR) or frequency (proportion). *p-values based on Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables.

RESULTS

Table 1 depicts patient and disease characteristics based on salvage treatment for both the initial 444 patients available for analysis, and the final cohort of 378 patients use in our analysis. Among the 444 patients, there were statistically significant differences in all characteristics between treatment groups: patients in the SA group overwhelmingly underwent EBRT (92% vs. 57%) as their primary treatment, had higher PSA measurement prior to salvage treatment (4.5 ng/ml vs. 3.7 ng/ml), and lower Gleason score prior to salvage treatment (26% had Gleason grade ≤6 vs. 11%) compared to the SRP group. Using propensity score methodology, patients with propensity scores at the extremes were excluded, which minimized differences in many of these characteristics (Table 1). To further illustrate the minimized differences in characteristics between treatment groups, patient characteristics after adjusting for propensity score are shown in Table 2.

Among our reduced cohort of 378 patients, 48 died from their disease. The median followup time for survivors is 6.0 (interquartile range [IQR] 3.0, 9.7) years from salvage treatment. Eighty-eight patients developed metastasis, and the median followup time among patients free from metastasis is 4.6 (IQR 2.3, 7.9) years from salvage treatment. We saw non-significant higher rates of CSS (HR 1.02, 95% CI 0.51, 2.06, p=0.9) (Figure 2A) and non-significantly better MFS (HR 0.71, 95% CI 0.44, 1.13, p=0.15) (Figure 2B) among patients undergoing SA compared to patients undergoing SRP.

Table 2. Patient characteristic based on salvage treatment, adjusted for propensity score[1]

	Final cohort in analysis (N=378)		
	Radical prostatectomy (n=208; 55%)	Ablation (n=170; 45%)	p[2]
External beam only as primary radiation treatment	76%	78%	0.5
Age at salvage treatment (years)	66.7	66.8	0.9
Hormonal treatment prior to salvage treatment	37%	45%	0.2
PSA prior to salvage treatment (ng/ml)	5.2	5.2	>0.9
Gleason score prior to salvage treatment ≥7	86%	88%	0.5

All results are mean and proportion. [1]Adjustments were carried out by using a logistic regression model with treatment type as the outcome, patient characteristic and propensity score as the predictor, then providing estimates when the propensity score set at the mean. [2]p-values reflect the difference between groups after adjusting for propensity score. PSA: prostate-specific antigen.

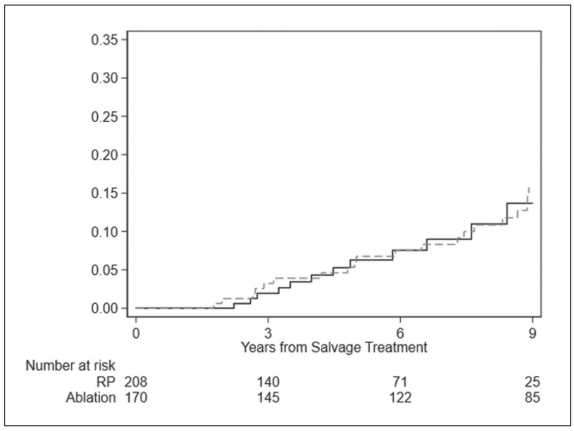

Figure 2A. Kaplan-Meier estimated cumulative incidence curve depicting cancer-specific death for salvage radical prostatectomy (solid black line) and salvage ablation (dashed gray line).

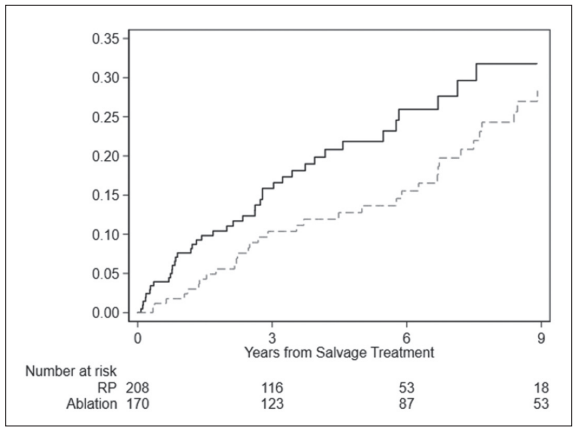

Figure 2B. Kaplan-Meier estimated cumulative incidence curve depicting metastasis for salvage radical prostatectomy (solid black line) and salvage ablation (dashed gray line).

These results prompted additional exploration into months from diagnosis of metastasis to death or last followup among patients developing metastasis. We found that patients undergoing SA had shorter duration between metastasis and last followup compared to patients undergoing SRP (median 1.1 years vs. 2.3 years, respectively, p=0.027), suggesting the possibility of more regular followup in patients undergoing SRP prompting earlier identification of metastasis.

Among the 377 patients with available information, 143 received hormonal treatment after their salvage therapy. There were higher rates of ADT following SA vs. SRP (HR 1.42, 95% CI 0.97, 2.08, p=0.068). Figure 3 depicts the adjusted probability of receipt of hormonal therapy after salvage treatment for a patient at the mean propensity score, where we can see that the three-year rate of ADT is 30% following SA and 23% following SRP. The three-year rate of ADT prior to metastasis is 29% and 16% for patients undergoing SA and SRP, respectively.

DISCUSSION

This study compares the oncologic outcomes of two cohorts of patients treated for locally recurrent prostate cancer following radiation therapy, using propensity score matching to balance key characteristics between the comparator groups to minimize potential bias. We found no statistically significant differences in MFS, CSS, and time to ADT therapy initiation. Biochemical recurrence-free survival (BRFS) was not evaluated due to the inherent differences in the definitions of biochemical recurrence in the post-surgical and post-ablative settings.

However, the upper-bound of the CI around the HR of ADT initiation in our study suggests that ADT was used more frequently after treatment in patients who underwent SA at UWO, while there was a non-statistically significantly improved MFS. Given this finding, we evaluated whether these results could be due to differences in the clinical treatment strategies employed by the two institutions with regards to the timing of ADT initiation. Notably, while the three-year rate of ADT is 30% following SA and 23% following SRP, rates of ADT prior to metastasis were 29% following SA and 16% following SRP. This indicates that different clinical inflection points may have been used to prompt ADT initiation, which may have contributed to the observed differences in both the time to ADT initiation and the MFS.

Additionally, an exploratory analysis indicates that the MFS could be, in part, due to differing followup regimens between the groups, and is a further limitation to this analysis. Despite this potential divergent treatment regimen, the CSS is nearly identical between the two cohorts.

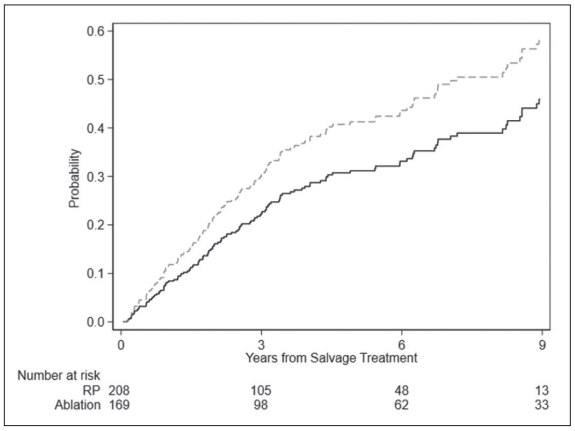

Figure 3. Adjusted cumulative incidence curve depicting hormonal treatment after salvage radical prostatectomy (RP) (solid black line) and salvage ablation (dashed gray line) with propensity score at the mean.

Multiple other studies have independently evaluated the oncologic efficacy of the therapeutic modalities evaluated here. A multi-institution evaluation of the results of SRP in 404 patients identified 10-year MFS and CSS of 77% and 83%, respectively, which are comparable to those in the SRP cohort reported here.[4]

The published reports for SA cohorts are less mature but also provide supporting evidence. Crouzet et al evaluated the results of 290 men who underwent salvage HIFU, finding seven-year CSS and MFS of 80%, while 60% of the patients required the initiation of ADT.[9]

Another, more recent publication evaluated the outcomes of 150 men treated with salvage HIFU and showed a three-year MFS of 91%, a 97% CSS, and a 41% rate of ADT initiation.[10]

A recent pooled analysis of 286 patients from UWO and MD Anderson, which included the UWO patients from this analysis, showed a 10-year CSS of 81% and 69% rate of ADT initiation. The MFS, CSS, and rates of ADT initiation seen in these SA studies are comparable to the findings here.

Finally, a recent metanalysis reviewed the findings of 150 individual studies that evaluated the use of SRP, HIFU, cryotherapy, stereotactic body radiation, low-dose-rate brachytherapy and high-dose-rate brachytherapy, and found a 50–60% five-year recurrence-free survival depending on the therapy employed.[15] This study also identified no statistically significant differences between SRP and the other therapies evaluated.

Limitations

There are several limitations to the current study.

First, this is a retrospective analysis of two patient cohorts treated at separate institutions. There are likely to be different institutional practices with respect to prostate cancer management. These may have included the timing of followup visits and imaging studies, which may have contributed to variation in the time to oncologic outcomes.

Additionally, the time periods of treatment in the two cohorts differed, with 67% of the SA patients in the comparison cohort being treated between 1995 and 2004, compared with only 18% of the SRP cohort undergoing treatment during this time, making the SRP cohort more contemporary. This may have affected the spectrum of subsequent therapeutics used upon prostate cancer relapse, in addition to potentially contributing to differences in the underlying primary radiation regimens used in each of the patient cohorts.

Also, while the propensity score matching used herein attempted to minimize the difference in baseline patient characteristics, including the pre-salvage PSA, pre-salvage Gleason score, and primary radiation treatment, unmeasured confounding likely remains.

Finally, despite the propensity score matching, there remained a difference in the primary radiation therapeutic modality employed in the salvage groups, with 93% of the SA group receiving EBRT, compared with only 63% of the SRP group. This primarily represents the fact that 70% of the SA group were treated from 1995–2004, at which time the preferred radiation modality in Canadian centers was EBRT. SA therapies have been shown to also be technically feasible in patients with post-brachytherapy failures, without significant technological barriers.[16] Collectively, however, the totality of these factors may have contributed bias to the analysis.

CONCLUSIONS

No significant differences in oncologic outcomes were identified between SA and SRP in two high-volume referral centers. Our study used propensity score matching to minimize potential bias, demonstrating that MFS and CSS in each group is excellent. SA or SRP offer potential curative therapy, with approximately 80% five-year MFS and 65% five-year ADT-free survival. Given that ADT is non-curative and has a significant side effect profile, SA or SRP should be strongly considered over ADT therapy alone in healthy men with clinically localized radio-recurrent prostate cancer. Future research may further elucidate subpopulations that may be more amenable to either SRP or SA.

COMPETING INTERESTS: Dr. McPherson has been an advisory board member for Knight and TerSera; and has received grants/honoraria from Abbvie, Bayer, Knight, and TerSera. Dr. Chin has been an advisory board member for Abbvie, Johnson & Johnson, TerSera, and Theralase; a consultant for Profound; and has participated in clinical trials supported by Astellas,

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This paper has been peer-reviewed.

REFERENCES

1. Catton CN, Lukka H, Gu C-S, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol* 2017;35:1884-90. https://doi.org/10.1200/JCO.2016.71.7397
2. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. *JAMA* 2005;294:1233-9. https://doi.org/10.1001/jama.294.10.1233
3. Gotto GT, Yunis LH, Vora K, et al. Impact of prior prostate radiation on complications after radical prostatectomy. *J Urol* 2010;184:136-42. https://doi.org/10.1016/j.juro.2010.03.031
4. Chade DC, Shariat SF, Cronin AM, et al. Salvage radical prostatectomy for radiation-recurrent prostate cancer: A multi-institutional collaboration. *Eur Urol* 2011;60:205-10. https://doi.org/10.1016/j.eururo.2011.03.011
5. Tetreault-Laflamme A, Crook J. Options for salvage of radiation failures for prostate cancer. *Semin Radiat Oncol* 2017;27:67-78. https://doi.org/10.1016/j.semradonc.2016.08.007
6. Williams AK, Martínez CH, Lu C, et al. Disease-free survival following salvage cryotherapy for biopsy-proven radio-recurrent prostate cancer. *Eur Urol* 2011;60:405-10. https://doi.org/10.1016/j.eururo.2010.12.012
7. Chin JL, Lavi A, Metcalfe MJ, et al. Long-term outcomes of whole gland salvage cryotherapy for locally recurrent prostate cancer following radiation therapy: A combined analysis of two centers. *J Urol* 2021;206:646-54. https://doi.org/10.1097/JU.0000000000001831
8. Jones TA, Chin J, McLeod D, et al. High-intensity focused ultrasound for radio-recurrent prostate cancer: A North American clinical trial. *J Urol* 199:133-9 https://doi.org/10.1016/j.juro.2017.06.078
9. Crouzet S, Murat F-J, Pommier P, et al. Locally recurrent prostate cancer after initial radiation therapy: Early salvage high-intensity focused ultrasound improves oncologic outcomes. *Radiother Oncol* 2012;105:198-202. https://doi.org/10.1016/j.radonc.2012.09.014
10. Kanthabalan A, Peters M, Van Vulpen M, et al. Focal salvage high-intensity focused ultrasound in radio-recurrent prostate cancer. *BJU Int* 2017;120:246-56. https://doi.org/10.1111/bju.13831
11. Siddiqui KM, Billia M, Arifin A, et al. Pathological, oncologic, and functional outcomes of a prospective registry of salvage high-intensity focused ultrasound ablation for radio-recurrent prostate cancer. *J Urol* 2017;197:97-102. https://doi.org/10.1016/j.juro.2016.06.092
12. Paparel P, Cronin AM, Savage C, et al. Oncologic outcome and patterns of recurrence after salvage radical prostatectomy. *Eur Urol* 2008;55:404-11. https://doi.org/10.1016/j.eururo.2008.07.007
13. Ng CK, Moussa M, Downey DB, et al. Salvage cryoablation of the prostate: Followup and analysis of predictive factors for outcome. *J Urol* 2007;178:1253-7. https://doi.org/10.1016/j.juro.2007.05.137
14. Haque R, UlcickasYood M, Xu X, et al. Cardiovascular disease risk and androgen deprivation therapy in patients with localized prostate cancer: A prospective cohort study. *Br J Cancer* 2017;117:1233. https://doi.org/10.1038/bjc.2017.280
15. Valle L, Lehrer E, Markovic D, et al. A systematic review and meta-analysis of local salvage therapies after radiotherapy for prostate cancer (MASTER). *Eur Urol* 2021;80:280-92. https://doi.org/10.1016/j.eururo.2020.11.010
16. Yutkin V, Ahmed HU, Donaldson I, et al. Salvage high-intensity focused ultrasound for patients with recurrent prostate cancer after brachytherapy. *Urology* 2014;84:1157-62. https://doi.org/10.1016/j.urology.2014.06.054

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