

Research Article

Comparison of Outcomes of Transrectal Ultrasound Guided Biopsy and Transperineal Template Guided Biopsy of Prostate in Patient on Active Surveillance for Low Risk Localised Prostate Cancer

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Submitted: 02 February 2019

Accepted: 06 September 2019

Published: 09 September 2019

ISSN: 2379-951X

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Keywords

- Active surveillance
- Prostate cancer, Gleason score
- PSA
- Template biopsy

Abstract

Introduction: The onset of PSA testing and low threshold for prostate biopsies, more people are diagnosed with prostate cancer. TRUS guided biopsies (10-12 cores) has been used as a standard in all prostate re-biopsies. With MRI scans detecting possible prostate cancer foci and the advent of template, the role of TRUS biopsy is questioned for those on AS.

Aim: To compare the outcomes of template and TRUS re-biopsy modes of patients on active surveillance and determine if template resulted in more significant histology upgrade and better cancer specific and overall survivals.

Methodology: The Somerset cancer registry was searched for patients on active monitoring. 371 patients were identified. Those on watchful waiting and those less than 12 months on AS were excluded, limiting the number to 231 patients. Data was collected from the Trust electronic system on inclusion criteria, follow up and outcomes.

Results: 155 patients had re-biopsy, 42 by TRUS, 99 by template and 14 had both. 19 (45%) out of 42 patients that had TRUS had histology upgrade. For template this was 34 (34%) and 6 (42%) out of 14 that had both biopsies had upgrade by template only. There is no statistical difference between both.

TRUS and template re-biopsy modes resulted in 100% cancer-specific survival. The survival probability for TRUS vs template at 8 years is 0.87 vs 0.95, this is statistically significant.

Conclusion: Outcomes of re-biopsy by TRUS compares favourably to that of template re-biopsy. Use of MRI-ultrasound fusion biopsy will enhance the result of TRUS biopsy.

ABBREVIATIONS

AS: Active Surveillance; TRUS: Transrectal Ultrasound; TTB: Template Biopsy

INTRODUCTION

The onset of prostate specific antigen (PSA) testing and low threshold for prostate biopsy has resulted in more people being diagnosed with prostate cancer in their life time [1]. Etzioni et al. [1], concluded that the observed trends in prostate cancer incidence are consistent with considerable overdiagnosis among PSA detected cases.

Active surveillance can be a good choice for those with

low risk, disease compared to substantial morbidity of radical treatment. Hayes et al., a decision analysis study compared the quality of life benefits and risk of active surveillance compared with initial treatment radical treatment in men with low risk disease. Their main outcome measure was quality-adjusted life expectancy (QALE). Active surveillance was found to have the greatest QALE compared to radical treatment.

The study aimed to determine 1) if template re-biopsy caused more histology upgrade significant enough to abandon active surveillance when compared to TRUS re-biopsy. 2) Is there a significant difference in the cancer specific survival and overall survival in those that TTB and TRUS re-biopsy? 3) If there is

correlation between repeat biopsy compared to final pathology for those patients that had radical prostatectomy?

NICE guidelines on prostate cancer (CG 175), did not advise on the type of repeat biopsy to offer. Traditionally, transrectal ultrasound (TRUS) guided biopsies (10-12 cores) has been used as a standard in all repeat prostate biopsies. Deficiencies with use of TRUS biopsies are made more obvious with advent of multi-parametric MRI scan and template biopsy.

Hu et al. [3], in a biopsy simulation study concluded that the accuracy of template biopsy (TTB) is approximately 0.90 (AUC) compared to that of TRUS which varied between 0.7-0.8 (AUC).

Scott et al. [4], in a retrospective study of 431 patients who had radical prostatectomy, compared the degree of upgrading and increase in clinical risk category of TTB to TRUS. In terms of upgrading, 33.2% of TRUS vs 30.41% TTB were upgraded, which was not significantly different (P=0.55). TTB was more reflective of the actual clinical risk category, with TRUS biopsy more likely to show an increase in clinical risk (TRUS 22.3% vs TTB14.2%, P = 0.04).

Because TTB ability to predict more accurately the clinical risk category it has become more acceptable for prostate re-biopsy. But is there any benefit in routinely offering template re-biopsy to all patients on active surveillance when considering the cost implications and the delays in meeting target? Is there any cancer specific survival or overall survival benefit attributable to routinely offering template?

Romero-Otero et al. [5], in a review article stated that at 10 years, active surveillance appear to reduce overtreatment with low risk prostate cancer without appearing to compromise cancer specific survival. In a systematic review, Aboumohamed et al. [6], a total of 24 studies comprising of 9920 patients on active surveillance were included. The median follow up years was 3.3 (1.5-6.4). There were 21 prostate cancer deaths and 42 metastasis in 38,311 person-years of follow up. When Gleason 7 disease was excluded, this fell to 6 prostate cancer specific deaths and 14 metastasis in 21182 person-year follow up.

Active surveillance based on re-biopsy using TRUS guidance has shown itself to be effective in management of patents on active surveillance for low risk prostate cancer as long as other factors are taking into consideration. Such factors include the Gleason grade, PSA velocity MRI outcome and patient wishes. It is also clear from the above that Gleason score above 7 at the initial biopsy have adverse effect on the outcome of patients on active surveillance.

MATERIALS AND METHODS

This study is a retrospective study related to a single institution. The Somerset cancer registry was searched from 2008 when recording started for patients on active monitoring for prostate cancer; this yielded a total of 371 patients up to December 2015. A total 231 patients were included in the study for analysis after excluding those on watchful waiting and those less than 12 months on active surveillance. All information records regarding this study were stored on the Trust IT system which is password protected.

The source of the information for the study were the Trust electronic document management and record system (EDMS), the admissions, diagnosis and treatment (ADT) system, and the radiology PAC system. Radical treatment as related to prostate cancer is centralised in the region. EDMS provided records for almost all the patients that had radical radiotherapy as the oncology centre keeps the responsible consultant updated. Information relating to radical prostatectomy was obtained from MDT co-ordinator of the treating hospital.

Data were collected on the excel spreadsheet on three broad categories. The categories were the inclusion criteria for enrolment into active surveillance, the events of the active surveillance and the events occurring post active surveillance. There were categorical and continuous data generated in this study, statistical methods like mean, mode and range were used to analyze data. Chi square test was used to evaluate categorical data and examine for statistical differences. Kaplan-Meier survival curve was used to determine overall survival over time as well as comparing that of different re-biopsy modes.

The biopsy protocol used by the unit is the 10 biopsy protocol for TRUS guided biopsy and 32 biopsy protocol for template biopsy. All the patients that had re-biopsy had MRI mainly before their biopsies. The active surveillance protocol follows the guidance stipulated by NICE. It should be noted that some of the patients who were under surveillance, were more suitable for treatment but preferred surveillance.

Active surveillance has undergone some changes since its inception within the unit; it is now more refined and adheres strictly to the NICE guidelines compared to period before 2008. Almost all the patients were still diagnosed with TRUS biopsy, and since 2011 all had template biopsy as the unit moves away from TRUS. This has created its own issues with target for re-biopsy at 12 months being missed some times.

RESULTS

General data description

The mean age at the time of diagnosis is 68.46 (52-81) years. Figure 1 shows, 95% of the patients have a performance score of 0 to 1; and 91% have ASA status of 1 to 2. Some patients with ASA 3 who are included were below age 65 years and have performance score of 0 or 1.

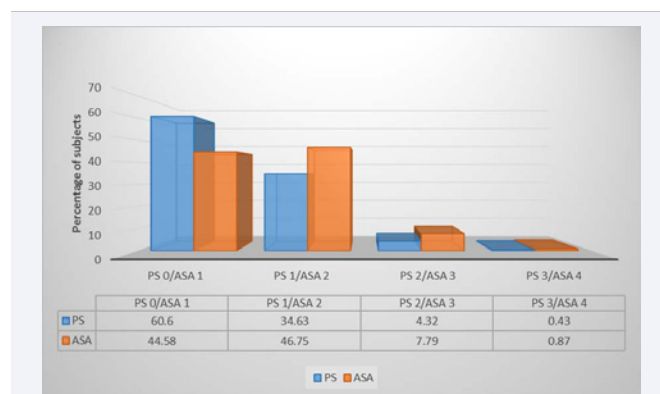


Figure 1 Showing distribution of performance and ASA status of patient entering active surveillance program.

166 patients (71.86%) were diagnosed with TRUS biopsy, whilst 39 patients (16.88%) were diagnosed following TURP and 26 patients (11.25%) were diagnosed with template biopsy following previous negative TRUS biopsy

139 patients (60.17%) were diagnosed as Gleason 3+3=6 disease and 79 patients (34.2%) were Gleason 3+4=7 (Table 1).

There were 34 patients with noted PSA above 10ug/L. Figure 2 illustrate the proportions of the patient with PSA above and below 10ug/L. Based on the histology, PSA and MRI outcome, a number of patients can be classed as not having low risk disease at the time of entry into active surveillance based on NICE guidelines (Table 2).

Histology outcome for repeat TRUS biopsies

19 patients (45.24%) out of the 42 had their histology upgraded. Out of the 19 patients, 14 upgrades were significant enough for them to have radical treatment. 13 patients (30.95%) did not have histology upgrade. Out of the 13 patients, 5 went on to have radical treatment based on other reasons. 10 patients (23.81%) showed histology downgrade or no cancer. 16 patients are still on active surveillance, and 7 have gone on to other outcomes (watchful waiting, hormone treatment or died). 19 patients in total had radical treatment (Tables 3 and 4).

Histology outcome for repeat Template biopsies

34 patients (34.34%) out of the 99 had their histology upgraded. Out of the 34 patients, 25 upgrades were significant enough for them to have radical treatment. 37 patients (37.37%) did not have histology upgrade. Out of the 37 patients, 13 went on to have radical treatment based on other reasons. 28 patients

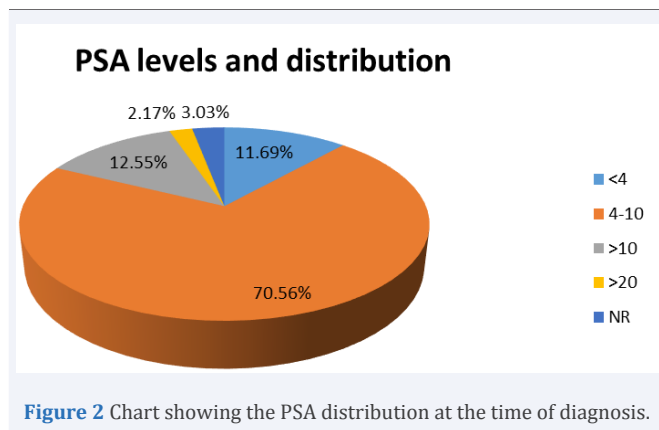


Figure 2 Chart showing the PSA distribution at the time of diagnosis.

(28.28%) showed histology downgrade or no cancer. 60 patients are still on active surveillance, and 1 have gone on to other outcomes. 38 patients had radical treatment (Tables 3 and 4).

Histology outcome for those that had both biopsies

14 patients had both TRUS and template repeat biopsies. There was no histology upgrade in 8 patients (57.14%), whilst in 6 patients (42.86%) template biopsy resulted in histology upgrade. 5 out of this 6 were significant enough for the patients to undergo radical treatment. This means a total of 43 patients had radical treatment following repeat template biopsies.

Statistical analysis relating to repeat biopsy outcome

The total number of patient that had TRUS biopsy is 56 and 19 had histology upgrade. 113 patients had template biopsy and

Table 1: Showing the outcome of histology on initial diagnosis.

| Gleason Score | Number | Number of Involved cores | Number | Percentage of cores involved | Number |
|---------------|-------------|--------------------------|------------|------------------------------|-------------|
| 3+3 | 139(60.17%) | 1 | 92(39.82%) | <5 | 119(51.52%) |
| 3+4 | 79(34.2%) | 2 | 42(18.18%) | <10 | 50(21.65%) |
| 4+3 | 6(2.6%) | 3 | 19(8.23%) | <15 | 12(5.19%) |
| No grade | 7(3.03%) | 4-5 | 10(4.33%) | 15-30 | 28(12.12%) |
| ----- | ----- | NR | 68(29.44%) | >30 | 5(2.16%) |
| ----- | ----- | ----- | ----- | NR | 17(7.36%) |
| Total | 231(100%) | | 231(100%) | | 231(100%) |

Abbreviations: NR= no record

Table 2: Table showing reasons for not being classed as low risk disease.

| Reasons | Number of patients | Percentage |
|--------------------------|--------------------|------------|
| PSA >10 | 14 | 6.06 |
| Gleason score 7 or above | 48 | 20.78 |
| MRI stage >T2a | 45 | 19.48 |
| GL 7 + PSA > 10 | 4 | 1.73 |
| GL 7 + MRI >T2a | 10 | 4.33 |
| PSA > 10 + MRI > T2a | 1 | 0.43 |
| Total | 122 | 52.81 |

Abbreviations: PSA: Prostate Specific Antigen; MRI: Magnetic Resonance Imaging; GL: Gleason Score

Table 3: Table summarizing the histology outcome for both re-biopsy mode.

| Re-biopsy mode | Histology upgrade | No change in grade | Histology downgrade | Total |
|----------------|-------------------|--------------------|---------------------|-----------|
| TRUS | 19 (45%) | 13 (31%) | 10 (24%) | 42 (100%) |
| Template | 34 (34.34%) | 37 (37.37%) | 28 (28.28%) | 99 (100%) |

Abbreviations: TRUS: Transrectal Ultrasound

Table 4: Table summarizing the overall outcome for both re-biopsy mode.

| Re-biopsy mode | Had radical treatment | Still on active surveillance | Other outcomes | Total |
|----------------|-----------------------|------------------------------|----------------|-----------|
| TRUS | 19 (45%) | 16 (38%) | 7 (17%) | 42 (100%) |
| Template | 38 (38%) | 60 (61%) | 1(1%) | 99 (100%) |

Abbreviations: TRUS: Transrectal Ultrasound

Table 5: Repeat biopsy histology that matched final pathology for patient that had radical prostatectomy.

| Re-biopsy mode | Number of patients that had radical treatment | Number matched to final pathology |
|-----------------------|---|-----------------------------------|
| Re-biopsy by TRUS | 3 | 0 |
| Re-biopsy by template | 16 | 8 |
| No re-biopsy | 3 | N/A |
| Total | 22 | 8 |

Abbreviations: TRUS: Transrectal Ultrasound

42 had histology upgrade. Using a 2x2 contingency table, the Chi-square statistics is 0.1704 and the P-value is 0.68. This result is not significant at P<0.05 between the outcome of repeat TRUS and template biopsies.

With respect to those that had radical amongst the two biopsy modes, 19 patients out of those that had TRUS re-biopsy had radical treatment and 43 of template re-biopsy had radical treatment. As above using the 2x2 contingency table, the chi-square statistics is 0.2742 and the P-value is 0.60. The result is not significant at P <0.05 between those of TRUS and template biopsy.

Anterior zone tumours

Of all the 43 patients that had radical treatment following repeat template biopsies, 14 (33%) had significant tumour found in the anterior zone only which influenced the decision to proceed to radical treatment (Figure 3). This represents 12.4% of 113 patients that had repeat template biopsy. Significant tumour is Gleason 3+4 or above and a large volume disease. The same Gleason grade must not be present in any other part of the prostate that can be biopsied by TRUS biopsy.

Comparing the outcome of the final pathology to the initial or repeat biopsy

Of the 22 final pathology specimen, 3 had re-biopsy by TRUS, whilst 16 had re-biopsy by template mode. 3 patients did not have re-biopsy (left active surveillance due MRI upstaging). Table 5 and Figure 3 compared the re-biopsy histology and final pathology.

Overall and Cancer specific mortality

At the end of this study 15 patients (6.49%) had died whilst on active surveillance. The average time to death is 4.62 (1.4-8.1) years. There were no prostate cancer related death. All

the patients died from complication of other illness, some of which are pre-existing prior to or diagnosed post entry into active surveillance. Figure 4 shows the survival probability for all patients using Kaplan-Meier curve, irrespective of re-biopsy mode.

10/15 (66.67%) patients had moved to watchful waiting prior to death; of the remaining 5 (33.33%), 3 patients had external beam radiotherapy and 2 had radical prostatectomy. The mean time to death for those that had radical treatment is 4.82 years from the time of diagnosis.

At the end of the study, 42 patients that had TRUS re-biopsy, 37 patients are alive and 5 dead, giving it overall survival of 88%. For template re-biopsy, 3 patients died giving it overall survival of 96%. Amongst the group that had both biopsy mode, 13

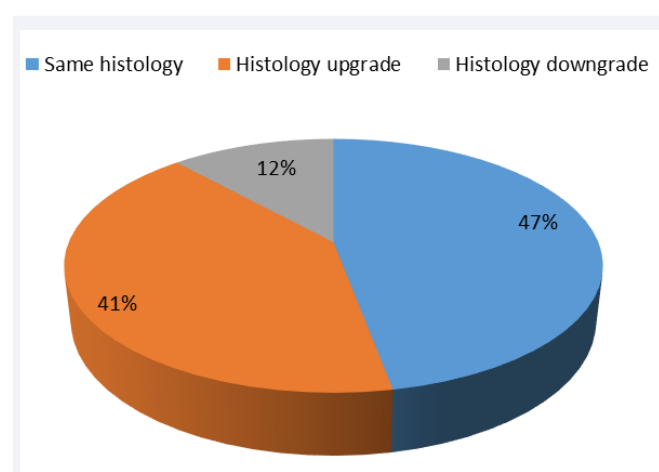


Figure 3 Comparison of final pathology to re-biopsy by template.

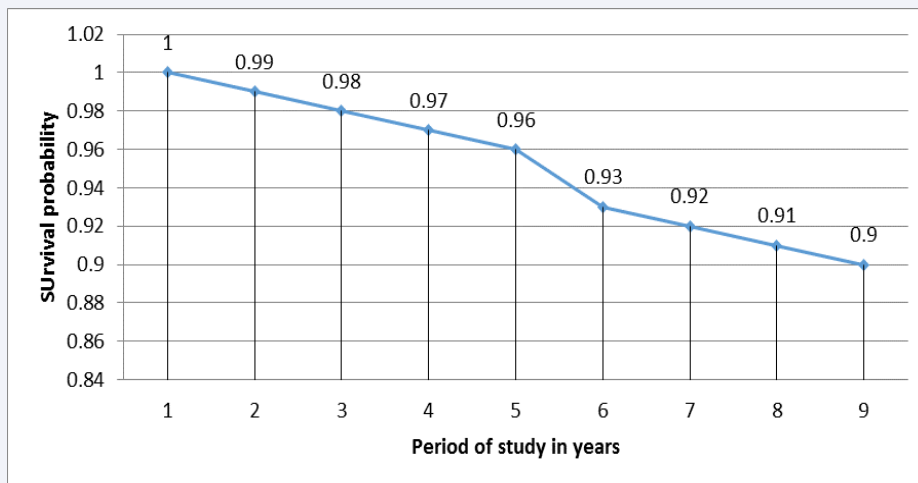


Figure 4 It shows survival curve for the entire patient (C.I 95%).

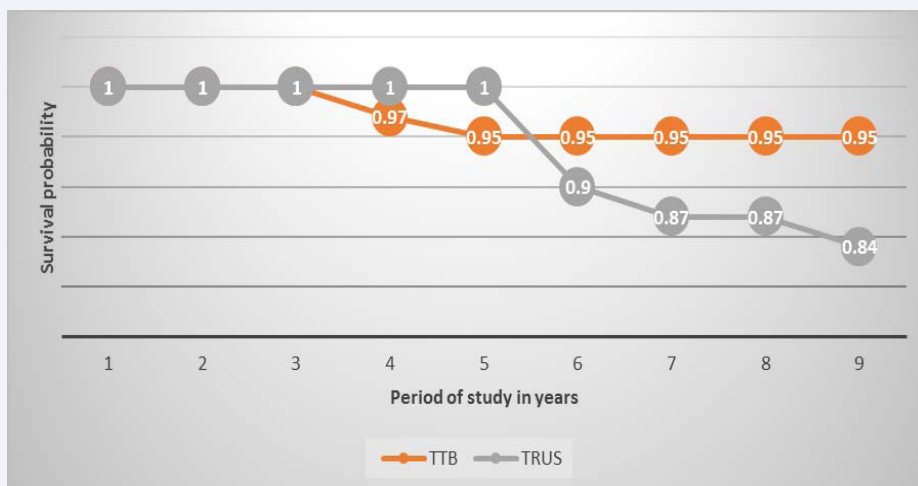


Figure 5 Figure showing the survival curve comparing the two re-biopsy modes.

patients are alive and 1 died from other cause, giving the overall survival of 92.21%.

Figure 5 shows the survival curve for both TRUS and template re-biopsy, with a P value of 0.037. The result is significant at $P < 0.05$. This means that the difference between the overall survivability in both arms is important.

DISCUSSION

This study noted that template re-biopsy resulted in more histology upgrade than TRUS re-biopsy, this was not statistically significant. Because only 14 out of 155 patients had both mode of re-biopsy, this study is unable to definitely say there is no difference in terms of histology upgrade produced by TRUS and template modes without further studies. Such study could be comparing the outcomes of MRI-TRUS fusion biopsy to that of template biopsy in the same patients.

This study has demonstrated no difference between cancer specific survivals in patients that had TRUS template re-biopsy. There is statistical difference in terms of overall survival between

the two re-biopsy modes, with template out performing TRUS. However, this may be due to most patients that had TRUS re-biopsy entered active surveillance at much earlier time and there is a selection bias in favour of offering healthier patient template re-biopsy as they are suited for radical treatment.

Comparing the outcome of repeat template biopsy histology and the final pathology, 8 (50%) out of the 16 patients matched on both sides with same Gleason score. There was also a significant number that were downgraded. Whether this is observer bias during the interpretation of the slides or the biopsied area showed a certain kind of Gleason grade, whilst the when the whole specimen is examined what may have being the dominant grade in a small (biopsy) sample becomes underrepresented in the whole gland? Because the pathologist that examine these specimen prior to final ratification at the MDT are quite experienced in it, we would then assume that core biopsy specimen are usually under representation of the total prostate specimen so accounting for the discrepancies in the final pathology and re-biopsy.

Role of various biopsy modes

Template biopsy in this study detected significant anterior cancer in 14 (12.4%) of all the 113 patients that had it. These tumours were not detected in any other part of the prostate, though there may be other lower grade tumour in the same prostate. This number represents 33% of 43 that had radical treatment. This is a significant finding in that if these patients did not have template biopsy they may have continued on active surveillance but with false confidence. Template biopsy is ideal for those patients whose pre biopsy MRI indicates presence of anterior tumour or any area that can be targeted by TRUS biopsy.

The study believes that the use of TRUS re-biopsy is something that should be mainstream rather than re-biopsy being all by template. As was noted before, TRUS and template re-biopsy modes produced 100% cancer specific survival and if the selection criteria is strict for TRUS as it is for those having template in terms of their fitness for radical treatment, then the overall survival should approach each other. Concerns with infection following TRUS biopsy should not be a hindrance to this. Raaijmaker et al. [7], and Rietbergen et al. [8], reported low grade fever in 3.5% and 4.2% and hospitalization rate of 0.5% and 0.4% post TRUS biopsy. MRI-Ultrasound fusion technology, means that TRUS biopsy can play a better role in initial biopsy for diagnosis and re-biopsy of those on active surveillance. Siddiqui et al. [9], and Vourganti et al. [10], both concluded that targeted biopsies with MRI TRUS fusion yields more higher grade cancer than standard biopsy for those that are having initial and repeat biopsies.

Strengths and limitations

The strengths of this study are that the start and end point are fixed, and cannot be manipulated, any outcome recorded are independent of any bias

The limitations of this study are that is a single institution study and retrospective. This means that the study was not designed in a specific way and manner as to answer a specific question. There were no measures to ensure that the outcomes of histology on re-biopsy were not influenced by tumour biology of individual patients. This would have been avoided if all the patients had both types of biopsy.

Though this study was retrospective, there was no data loss that would have compromised the outcome of the study; however, some of the radiology reporting of the MRI is sub optimal. Centralization of radical treatment did not affect the outcome of the study, as information regarding outcome of treatment were obtained from relevant treatment centres.

Implications for clinical practice

In the current NHS climate and drive for cost savings, it's difficult for all patients entering active surveillance to have re-biopsy by template means. This uses up theatre time and resources, this means longer waiting time and missing of target.

The study will encourage practitioners to evaluate their strategy of active surveillance and seek for ways to uses

resources better whilst maintaining good outcome for patients. Like mentioned before, one of the ways to do this is through the introduction of fusion biopsy technology. In those centres where template re-biopsy for patients on active surveillance has not been introduced, this study will serve to assure them about survivability of the patients in their care whilst at the same time highlighting ways to improve their practices.

CONCLUSION

This study has shown that repeat biopsies by TRUS mode for patients on active surveillance compares favourably with template biopsy in terms of histology upgrade and cancer specific survival.

Template biopsy offers great advantage when MRI scan detects anterior based tumour. They are more likely to detect significant tumour which otherwise will not be targetable by TRUS biopsy. Template biopsy offers assurance to both doctors and patients when the outcome of re-biopsy shows no cancer or low grade cancer on histology.

MRI-ultrasound fusion biopsy is the way forward for re-biopsy for active surveillance programme in terms of cutting waiting time and cost effectiveness whilst maintaining outcome comparable to template biopsy.

ACKNOWLEDGEMENTS

1. The library team at St Helens and Knowsley for helping with literature searches.
2. The Vicky Barnes, cancer tracking officer at St Helens and Knowsley for providing information from Somerset cancer registry on patients in active monitoring of prostate cancer.
3. Tom Herbert urology foundation doctor for helping with data collection on two occasions.
4. My wife, Chika, who provided some expert advice on using EXCEL to analyze data.
5. Michelle Bradley, cancer tracking RLBUTH for providing the information on outcome of patients that had radical prostatectomy.
6. My Supervisor, Mr. Mistry who kindly agreed to assume this role and provided advice through the entire specialist academic activity.
7. This study was done as part of ChM urology dissertation of University of Edinburgh, in combination with the Royal College of Surgeons of Edinburgh.

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Cite this article

Ejikeme C, Mistry R (2019) Comparison of Outcomes of Transrectal Ultrasound Guided Biopsy and Transperineal Template Guided Biopsy of Prostate in Patient on Active Surveillance for Low Risk Localised Prostate Cancer. *J Urol Res* 6(1): 1114.