Optimizing biopsy strategy for prostate cancer: Bayesian framework of network meta-analysis and hierarchical summary receiver operating characteristic model for diagnostic accuracy

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ABSTRACT
Overdiagnosis and overtreatment are well known problems in prostate cancer (PCa). The transrectal ultrasound (TRUS) Guided biopsy (GB) as a current gold standard investigation has a low positive detection rate resulting in unnecessary biopsies. The choice of optimal biopsy strategy needs to be defined. Therefore, we undertook a Bayesian network meta analysis (NMA) and Bayesian prediction in the hierarchical summary receiver operating characteristic (HSROC) model to present a method for optimizing biopsy strategy in PCa. Twenty eight relevant studies were retrieved through online databases of EMBASE, MEDLINE, and CENTRAL up to February 2020. Markov chain Monte Carlo simulation and Surface Under the Cumulative RAnking curve were used to calculate the rank probability using odds ratio with 95% credible interval. HSROC model was used to formulate the predicted true sensitivity and specificity of each biopsy strategy. Six different PCa biopsy strategies including transrectal ultrasound GB (TRUS GB), fusion GB (FUS GB), fusion + transrectal ultrasound GB (FUS + TRUS GB), magnetic resonance imaging GB (MRI GB), transperineal ultrasound GB (TPUS GB), and contrast enhanced ultrasound GB were analyzed in this study with a total of 7584 patients. These strategies were analyzed on five outcomes including detection rate of overall PCa, clinically significant PCa, insignificant PCa, complication rate, and HSROC. The rank probability showed that the overall PCa detection rate was higher in FUS + TRUS GB, MRI GB, and FUS GB. In terms of clinically significant PCa detection, FUS + TRUS GB and FUS GB had a relatively higher clinically significant PCa detection rate, whereas TRUS GB had a relatively lower rate for clinically significant PCa detection rate. MRI GB (91% and 81%) and FUS GB (82% and 83%) had the highest predicted true sensitivity and specificity, respectively, whereas TRUS GB (62% and 83%) had a lower predicted true sensitivity and specificity. MRI GB, FUS GB, and FUS + TRUS GB were associated with lower complication rate, whereas TPUS GB and TRUS GB were more associated with higher complication rate. This NMA and HSROC model highlight the important finding that FUS + TRUS GB, FUS GB, and MRI GB were superior compared with other strategies to avoid the overdiagnosis and overtreatment of PCa. FUS GB, MRI GB, and FUS + TRUS GB had lower complication rates. These results may assist in shared decision making between patients, carers, and their surgeons.

INTRODUCTION
Prostate cancer (PCa) is the second most common diagnosed malignancy in males worldwide, and the fifth leading cause of cancer death in men. Indonesia, PCa is the third most common urologic cancer in men according to the GLOBOCAN 2012 study.

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Currently, the worldwide usage of the diagnostic strategy of PCa consisting of serum prostate-specific antigen (PSA) measurement, digital rectal examination, and transrectal ultrasound-guided biopsies (TRUS-GB) has improved the detection rate of early PCa.\(^4\) The European Association of Urology, the US Preventive Services Task Force, and the UK National Institute for Health and Care Excellence suggest transrectal ultrasound (TRUS)-guided biopsy (GB) as a standard investigation in the diagnosis of PCa.\(^{10}\) However, this biopsy protocol resulted in a positive detection rate of only 17%–36%,\(^{6,7}\) with low sensitivity of 27%–40.3% which could easily carry a high rate of missed cancer.\(^8\) The dilemma being encountered by physicians was to decide whether or not to treat the patient in the initial setting of a negative prostate biopsy. Because PCa is often multifocal, the possibility exists that these patients may have cancer despite an initial negative biopsy. A significant number of patients (13%–41%) with persistently elevated PSA after an initial negative biopsy had a positive repeat biopsy suggesting that this method is associated with underdetection of high-grade PCa and overdetection of low-grade cancers. The ideal systematic biopsy strategy remains to be defined.\(^{9-12}\)

With the problem of overdiagnosis and overtreatment of PCa, several imaging-GB strategies had been utilized in an effort to increase the PCa detection rate.\(^{13}\) It is difficult to compare and provide the optimal biopsy strategy due to the absence of direct head-to-head statistical comparison and limited evidence. Therefore, we undertook the network meta-analysis (NMA) and anticipated it to provide a hierarchy of diverse methods in a wide spectrum of population.\(^{14,15}\) Six different PCa biopsy strategies, consisting of TRUS-GB, transperineal ultrasound-GB (TPUS-GB), contrast-enhanced ultrasound-GB (CEUS-GB), magnetic resonance imaging-GB (MRI-GB), fusion-GB (FUS-GB), and FUS-GB plus TRUS-GB, and five clinical outcomes, consisting of overall PCa detection, significant PCa detection, insignificant PCa detection, complication rate, and hierarchical summary receiver operating characteristics (HSROC), were analyzed in this study.

**METHODS**

**Literature search strategy and study selection**

Eligible articles were extracted from online databases including EMBASE, MEDLINE, and CENTRAL up to February 2020. The search strategy included two parts (PCa and biopsy strategy) using certain keywords in combination with Medical Subject Headings terms and words: “prostate cancer,” “biopsy strategy,” “targeted biopsy,” “systematic biopsy,” “TRUS-GB,” “TPUS-GB,” “FUS-GB,” “FUS + TRUS-GB,” “CEUS-GB,” and “MRI-GB.” Full texts and abstracts were initially and independently screened by two reviewers and were assessed according to inclusion and exclusion criteria. Insignificant studies were excluded. Discrepancies between two reviewers were settled in a discussion with a third reviewer. Ethical approval was not required because it did not contain individual patient’s data. The PICO of the study is explained in Table 1.

**Data extraction and quality assessment**

Studies included in this article met the following criteria: (1) subjects were patients with PCa; (2) the required data to formulate NMA and HSROC was available; (3) the comparison was between at least two different biopsy strategies; (4) the article was in English; and (5) studies were either randomized controlled trials (RCTs) or original studies. Two reviewers (IAR and IF) individually extracted and reviewed data based on study selection criteria using standardized, structured, and piloted extraction forms. The results were checked and discussed by IAR and IF to finalize the included studies. Any discrepancies were resolved in discussion with a third reviewer. For each included study, important information was extracted including author’s name, publication year, number of sample sizes, mean age, prostate volume, mean PSA level, study design, intervention, overall PCa detection rate, clinical significant PCa detection rate, insignificant PCa detection rate, complication rate, true positive, false positive, false negative, and true negative. If the required data could not be directly acquired from articles, it was manually calculated using available data according to studies.\(^{16,17}\) Table 2 demonstrates all of the above mentioned data. Cochrane Collaboration’s risk of bias tool was used to assess the appropriateness of the included studies and the strength of the evidence. The investigations of risk of bias consisted of (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Low, high, or unclear risk of bias was used for judgments. Risk of bias assessment is reported in Figure 1. Figure 2 shows a detailed literature search and selection process. Publication bias was examined by Begg’s and Egger’s tests.\(^{18}\)

**Outcomes**

Overall PCa detection rate, clinically significant PCa detection rate, insignificant PCa detection rate, complication rate, and HSROC were ultimately analyzed as endpoints.

**Table 1: PICO of the study**

| PICO | Description |
|------|-------------|
| Patient | Patient with clinical suspicion of prostate cancer (high PSA or abnormal DRE) |
| Intervention | TRUS-GB (6, 8, 10, 12, 15, and 18 cores), TPUS-GB, CEUS-GB, FUS-GB, MRI-GB, and FUS + TRUS-GB |
| Control | TRUS-GB (6, 8, 10, 12, 15, and 18 cores), TPUS-GB, CEUS-GB, FUS-GB, MRI-GB, and FUS + TRUS-GB |
| Outcome | Overall prostate cancer, clinically significant, insignificant detection rate, complication rate, sensitivity, and specificity |

PSA = Prostate-specific antigen, DRE = Digital rectal examination, TRUS = Transrectal ultrasound, GB = Guided biopsy, TPUS = Transperineal ultrasound, CEUS = Contrast-enhanced ultrasound, FUS = Fusion, MRI = Magnetic resonance imaging
Table 2: Baseline characteristics of selected studies

| Author, year | Intervention | True Positive (TP) | False Positive (FP) | False Negative (FN) | True Negative (TN) | Event Rate | Sample Size | Event Rate | Sample Size | Event Rate | Sample Size | Mean Age | Prostate volume | Mean PSA level | Study design |
|--------------|-------------|--------------------|---------------------|---------------------|-------------------|------------|-------------|------------|-------------|------------|-------------|----------|----------------|---------------|-------------|
| Ardeshr R Rastinehad, 2014 | MRI+TRUS (FUS) GB, TRUS GB 12 cores, FUS+TRUS GB | 38 | 13 | 7 | 35 | 53 | 105 | 47 | 105 | 6 | 105 | 65.8 | NA | 9.2 | RCT |
| Arnout Alberts, 2017 | TRUS GB 6 cores, MRI+TRUS (FUS) GB, TRUS GB 12 cores, MRI GB | 19 | 30 | NA | 130 | 49 | 179 | 19 | 179 | 30 | 179 | 73.2 | 48 | 4.3 | RCT |
| Christian Arsov, 2015 | -MRI GB, MRI+TRUS (FUS) GB, FUS+TRUS GB | 31 | 8 | NA | 67 | 39 | 106 | 31 | 106 | 8 | 106 | 66.4 | 10 | 10 | RCT |
| Eduard Baco, 2015 | MRI+TRUS (FUS) GB, TRUS GB 12 cores, MRI GB | 38 | 13 | 7 | 35 | 51 | 86 | 38 | 86 | 13 | 86 | 65.4 | 43 | 7.4 | RCT |
| Ethan J Halpern, 2005 | CEUS GB, TRUS GB 6 cores, MRI+TRUS (FUS) GB, TRUS GB 10 cores | 1 | 10 | 2 | 93 | 11 | 301 | 1 | 301 | 10 | 301 | 63.4 | >4 | 9.5 | RCT |
| Francesco Porpiglia, 2016 | MRI+TRUS (FUS) GB, TRUS GB 12 cores, TRUS GB 10 cores, TRUS GB 12 cores | 47 | 7 | NA | 53 | 54 | 107 | 47 | 107 | 7 | 107 | 64.3 | 462 | 5.9 | RCT |
| Francesco Rodriguez-Covarrubias, 2011 | MRI+TRUS (FUS) GB, TRUS GB 12 cores, TRUS GB 10 cores, MRI+TRUS (FUS) GB | 26 | 10 | NA | 69 | 23 | 97 | 21 | 97 | 2 | 97 | 65.4 | 58 | 7.5 | RCT |
| Geoffrey A. Sonn, 2014 | CEUS GB, TRUS GB 12 cores, MRI+TRUS (FUS) GB, TRUS GB 12 cores, MRI+TRUS (FUS) GB | 54 | 58 | 46 | 42 | 31 | 100 | NA | NA | NA | NA | 65.9 | 25-9.9 | 9.9 | RCT |
| Gianluigi Taverna, 2011 | TRUS GB 12 cores, MRI+TRUS (FUS) GB, CEUS GB | 15 | 9 | 9 | 76 | 24 | 100 | 15 | 100 | 9 | 100 | 64.4 | NA | 12.63 | RCT |
| Gianluigi Taverna, 2015 | TRUS GB 12 cores, MRI+TRUS (FUS) GB, TRUS GB 12 cores | 12 | 14 | NA | 74 | 26 | 100 | 12 | 100 | 14 | 100 | 64.2 | 33 | 10 | Cohort |
| Haifeng Huang, 2016 | TRUS-GB, TPUS-GB, TRUS GB 6 cores, TRUS GB 12 cores, MRI+TRUS (FUS) GB, TRUS GB 15 cores | 38 | 25 | NA | 59 | 63 | 122 | 38 | 122 | 25 | 122 | 67.8 | 37 | 6.6 | RCT |
| M.A. Rochester, 2008 | TRUS GB 12 cores, TRUS GB 12 cores, TRUS GB 15 cores, MRI+TRUS (FUS) GB, TRUS GB 6 cores | 31 | 19 | NA | 72 | 50 | 122 | 31 | 122 | 19 | 122 | 68.2 | NA | 8.2 | RCT |
| Mahyar Ghafoori, 2015 | TRUS GB 12 cores, TRUS GB 12 cores, TRUS GB 18 cores, MRI+TRUS (FUS) GB | 4 | 9 | NA | 37 | 13 | 50 | 4 | 50 | 9 | 50 | 52.3 | 35 | 3.2 | RCT |
| Michael Mitterberger, 2007 | TRUS GB 12 cores, CEUS GB | 8 | 8 | NA | 34 | 16 | 50 | 8 | 50 | 8 | 50 | 54.8 | NA | 9.2 | RCT |

Contd...
### Table 2: Contd...

| Author, year | Interventions | Mean PSA level | Mean Prostate volume | Significant PCa detection rate | Clinical PCa detection rate | Insignificant PCa detection rate | Event Size | Sample Size | Mean Age | Size Positive (TP) | Size False Positive (FP) | Size True Negative (TN) | Size False Negative (FN) |
|--------------|---------------|----------------|----------------------|------------------------------|----------------------------|-------------------------------|------------|-------------|-----------|-------------------|-----------------------|--------------------------|------------------------|
| Rahman, et al. 2020 | TRUS-GB       | 9.3            | 45                   | 65                           | 100                         | 46                            | 11.3       | 65          | 56.3     | 107               | 19                    | 107                      | 97                     |
| Olivier Wegelin, 2019 | MRI-GB       | 9.1            | 60                   | 64                           | 100                         | 44                            | 11.3       | 64          | 40.6     | 88               | 19                    | 107                      | 90                     |
| P. Emiliatos, 2003 | TRUS GB 12 cores | 9.2            | 60                   | 65                           | 100                         | 44                            | 11.3       | 65          | 34.6     | 107               | 15                    | 107                      | 73                     |
| Roger Paul, 2006 | MRI-GB       | 9.4            | 50                   | 64                           | 100                         | 44                            | 11.3       | 64          | 40.1     | 88               | 19                    | 107                      | 90                     |
| Suneel Sridhar, 2008 | TRUS GB 12 cores | 9.5            | 60                   | 64                           | 100                         | 44                            | 11.3       | 64          | 75.1     | 107               | 55                    | 248                      | 36                     |
| Young Hyo Choi, 2019 | MRI + TRUS (FUS) GB | 9.6            | 60                   | 64                           | 100                         | 44                            | 11.3       | 64          | 40.1     | 88               | 19                    | 107                      | 90                     |

### RESULTS

#### Search results and included strategies

A total of 248 citations retrieved by search strategy were included in this NMA study. Then, full-text screen was conducted, and 86 studies were excluded because of reviews, case report, duplicates, and non-English language. Thirty-two articles were excluded after titles and abstract reading. Thirteen articles were removed after full-text review. Finally, 28 studies fulfilled the inclusion criteria consisting of a total of 6768 patients who were eligible and added for further analysis. All included studies were RCTs.

Several different strategies consisted of TRUS-GB, MRI-GB, MRI + TRUS (FUS) GB, US-Guided biopsy, TRUS-Guided biopsy, MRI + TRUS (FUS) GB, and TPUS-GB. Five endpoints were ultimately analyzed including overall PCA detection, clinically significant PCA detection, insignificant PCA detection, complication rate, and HSRCC. The flowchart of the study search and selection procedure is shown in Figure 2. The network structure graph is shown in Figure 3.

#### Overall prostate cancer detection rate

The results of overall PCA detection rate were analyzed by...
calculating 17 studies\cite{20-22,25,28,29,31-33,35-40,42,43} with the total of 7071 patients consisting of 6 biopsy strategies including TRUS-GB, FUS + TRUS-GB, MRI + TRUS (FUS)-GB, MRI-GB, TPUS-GB, and CEUS-GB, and network structure diagrams are shown in Figure 3a. The comparison of efficacy between different biopsy strategies for OR and 95% CI is presented in league table Figure 4a. As shown in the result with TRUS-GB as a comparator, FUS + TRUS-GB (RR: 1.35, 95% CrI: 0.8–2.2) was slightly better than MRI-GB (RR: 1.28, 95% CrI: 0.9–1.78) and FUS-GB (RR: 1.23, 95% CrI: 0.93–1.61). The cumulative rank probability based on SUCRA value showed that the biopsy strategies from best to worst in terms of overall PCa detection rate were FUS + TRUS-GB, MRI-GB, MRI + TRUS (FUS)-GB, TPUS-GB, CEUS-GB, and TRUS-GB. Figure 5a is a cumulative rank plot with the SUCRA of each strategy and its detailed ranking values are summarized in Table 3a.

**Clinically significant prostate cancer detection rate**

Fourteen studies\cite{20-22,25,28,29,32,33,35-38,40,42} with a total of 7830 patients were used to contribute to the analysis of clinically significant PCa detection rate. Figure 3b presents the network structure diagrams. The efficacy of each biopsy strategy was compared to each other and is presented in league table Figure 4b. Our analysis showed that in the case of TRUS-GB as reference, FUS-GB (RR: 1.51, 95% CrI: 0.87–2.61) was better than FUS + TRUS GB (RR: 1.47, 95% CrI: 0.55–3.89), TPUS-GB (RR: 1.2, 95% CrI: 0.23–6.1), and MRI-GB (RR: 1.09, 95% CrI: 0.56–2.15). As indicated by

| Study | SUCRA (%) |
|-------|-----------|
| A      |           |
| FUS + TRUS GB | 75.66 |
| MRI GB      | 70.76 |
| MRI + TRUS (FUS) GB | 65.36 |
| TPUS GB    | 33.95 |
| CEUS GB    | 29.15 |
| TRUS GB    | 25.13 |
| B      |           |
| MRI + TRUS (FUS) GB | 74.63 |
| FUS + TRUS GB | 67.03 |
| TPUS GB    | 51.56 |
| MRI GB | 43.63 |
| TRUS GB    | 33.27 |
| CEUS GB    | 29.88 |
| C      |           |
| CEUS GB | 75.14 |
| TRUS GB | 59.08 |
| TPUS GB | 59.06 |
| FUS + TRUS GB | 57.96 |
| MRI + TRUS (FUS) GB | 26.01 |
| MRI GB | 22.72 |
| D      |           |
| TPUS-GB | 91.98 |
| TRUS-GB | 63.06 |
| FUS-GB | 42.37 |
| FUS + TRUS-GB | 39.4 |
| MRI-GB | 13.2 |

SUCRA = Surface Under Cumulative RAning curve, TRUS = Transrectal ultrasound, GB = Guided biopsy, TPUS = Transperineal ultrasound, CEUS = Contrast-enhanced ultrasound, FUS = Fusion, MRI = Magnetic resonance imaging.
the results of ranking analysis based on SUCRA which is shown in Figure 5b and Table 3b, FUS-GB, FUS + TRUS-GB, TPUS-GB, MRI-GB, TRUS-GB, and CEUS-GB were ranked from best to worst, respectively.

**Insignificant prostate cancer detection rate**
The efficacy of each biopsy strategy in terms of insignificant PCa detection was also analyzed. Fourteen trials[^20-22,25,28,29,32,33,35-38,40,42] with a total of 6267 patients were used to analyze this endpoint. The detailed comparison was served in network structure diagrams in Figure 3c. Moreover, the efficacy of different biopsy strategies was compared to each other and is shown in league table Figure 4c. It was found that for TRUS-GB as a comparator, CEUS-GB (RR: 1.3, 95% CrI: 0.50–3.63) and TPUS-GB (RR: 1.11, 95% CrI: 0.22–5.52) were more associated with insignificant PCa detection compared to MRI-GB (RR: 0.67, 95% CrI: 0.33–1.32) and FUS-GB (RR: 0.71, 95% CrI: 0.39–1.24) which were more less associated with insignificant PCa detection. The results of SUCRA rank probability Figure 5c sorting from more associated to less associated with insignificant PCa detection were CEUS-GB, TRUS-GB, TPUS-GB, FUS + TRUS-GB, FUS-GB, and MRI-GB. The detailed SUCRA values are shown in Table 3c.
Figure 4: Network meta-analysis using odds ratio with 95% credible intervals of different biopsy strategies. A blue cell indicates that a treatment performed better than its comparator (estimate greater than 1), while an orange cell indicates that the treatment performed worse than its comparator (estimate smaller than 1). The strategy has been sorted from left to right according to Surface Under the Cumulative RAnking curve as from worst to best, respectively. (a) Overall prostate cancer outcome detection rate outcome, (b) Clinically significant prostate cancer detection rate outcome, (c) Insignificant prostate cancer detection rate outcome, (d) Complication rate
Complication rate
The evaluation of complication rate in relation to different biopsy strategies was also analysed. Eight studies with a total of 2073 patients contributed within the analysis of the results. The comparison of biopsy strategies was served in network structure diagram presented in Figure 3d and network league table presented in Figure 4d. Our analysis found that in TRUS-GB as reference, MRI-GB (RR: 0.66, 95% CrI: 0.55–0.78), FUS + TRUS-GB (RR: 0.67, 95% CrI: 0.07–6.1), and FUS-GB (RR: 0.83, 95% CrI: 0.61–1.13) were more related to lower complication rate compared to TPUS-GB (RR: 1.16, 95% CrI: 1.07–1.27) which was more related to high complication rate. Finally, the detailed rank probability showed that TPUS-GB, TRUS-GB, FUS-GB, FUS + TRUS-GB, and MRI-GB were ranked from higher to lower complication rate, respectively, with TPUS-GB and TRUS-GB related to higher complication, as presented in Table 3d and Figure 5d. The complications among the patients include infection/fever, pain, bleeding, rectal hemorrhage, hematuria, hemospermia, sepsis, and urinary retention, as shown in Table 4. Major complications of sepsis and urinary retention mostly occurred in TRUS-GB.

Hierarchical summary receiver operating characteristics
Data extraction showed a large heterogeneity in the reporting of diagnostic accuracy measures. For such reasons, the average operating points (summary of sensitivity and specificity) with the corresponding 95% CI were computed using the summary receiver operating characteristic curves using the hierarchical model proposed by Rutter and Gatsonis. Due to limited primary data, only four HSROC curves consisting of TRUS-GB, FUS-GB, MRI-GB, and CEUS-GB were managed to be analyzed. It is easily found that MRI-GB (91% and 81%) and FUS-GB (82% and 83%) presented the highest predicted sensitivity and specificity for overall PCa detection. CEUS-GB had the sensitivity and specificity of 74% and 82%, respectively; meanwhile, TRUS-GB had the lowest predicted sensitivity of 62% and specificity of 83%. Figure 6 summarizes the HSROC curve.

DISCUSSION
A key issue in the diagnosis and treatment of PCa is the need to detect PCa which is clinically significant and requires treatment. Although the gold standard for PCa is TRUS-GB, it is beset with problems of overdiagnosis and overtreatment.

To the best of our knowledge, this is the first study to combine Bayesian framework in NMA and HSROC model in biopsy strategy for PCa detection. Even in the case of limited primary evidence, all relevant evidences of biopsy strategy in PCa patients were integrated simultaneously by performing NMA. Moreover, to ensure a sustainable conclusion, we analyzed the sensitivity and specificity of biopsy strategy in the form of Bayesian prediction in HSROC. Bayesian framework was used to enhance the quality of our analysis so that it could provide results with more confidence for decision-making.

In terms of overall PCa and clinically significant PCa detection rate outcome, FUS + TRUS-GB, MRI-GB, and
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Table 4: Complication-related side effects in different biopsy strategies

| Author, year | Intervention | Complications | Total patients | Bleeding | Rectal hemorrhage | Hematuria | Hemospermia | Fever | Pain | Urinary retention | Sepsis |
|--------------|--------------|---------------|----------------|----------|-------------------|-----------|-------------|-------|------|------------------|-------|
| Nina Egbers, 2015 | MRI-GB       | 45            | 28             | 45       | 28                | 7         | 23          | 23    | 28   | NA                | NA    |
|               | TRUS-GB      | 36            | 36             | 45       | 35                | 6         | 34          | 34    | 7    | NA                | NA    |
| Haifeng Huang, 2016 | TRUS-GB      | 115           | 115            | 144      | 111               | 2         | 47          | 47    | 11   | NA                | 13    |
|               | TPUS-GB      | 94            | 94             | 98       | 91                | 0         | 35          | 35    | 2    | NA                | 10    |
| Le-Hang Guo, 2015 | TPUS-GB      | 73            | 73             | 87       | 75                | 0         | 33          | 33    | 2    | NA                | 6     |
|               | TRUS-GB      | 76            | 76             | 90       | 67                | 0         | 37          | 37    | 2    | NA                | 11    |
| Olivier Wegelin, 2019 | MRI-GB       | 52            | 52             | 69       | 40                | 2         | 47          | 47    | 2    | NA                | 16    |
|               | TRUS-GB      | 77            | 77             | 90       | 77                | 0         | 77          | 77    | 3    | NA                | 26    |
| Arthur R. Alberts, 2017 | TRUS-GB     | 120           | 120            | 144      | 118               | 0         | 11          | 11    | 2    | NA                | 27    |
|               | FUS-GB       | 129           | 129            | 158      | 129               | 0         | 129         | 129   | 0    | NA                | 48    |
| Christian Arsov, 2015 | MRI-GB       | 2            | 2              | 106      | 0                 | 0         | 2           | 2     | 0    | NA                | NA    |
|               | FUS + TRUS-GB| 1            | 1              | 104      | 0                 | 0         | 1           | 1     | 0    | NA                | NA    |
| Ryoei Hara, 2008 | TPUS-GB      | 23            | 23             | 126      | 126               | 0         | 2            | 2     | 2    | NA                | 1     |
| V. Kasivisvanathan, 2018 | MRI-GB     | 18            | 18             | 252      | 30                | 0         | 64          | 64    | 0    | NA                | NA    |
|               | TRUS-GB      | 129           | 129            | 248      | 129               | 0         | 129         | 129   | 0    | NA                | 45    |

MRI + TRUS (FUS)-GB were ranked as the best. As for TRUS-GB, it was more associated with lower overall PCa detection and was more inferior in clinically significant PCa detection. MRI examination before prostate biopsy has the advantages of showing the location of the lesion; thus, it provides high sensitivity for detecting PCa. Clinicians’ choice of the appropriate biopsy might be influenced by MRI. On T1-weighted images, PCa typically appears as a low signal within areas of homogeneous high signal. On T2-weighted sequences, suspicious areas of the prostate could also be detected. Another study has also emphasized the potential value of combining MRI with ultrasound-GB/FUS-GB. High-resolution imaging and the better ability to detect cancer at a higher rate per core were shown in FUS-GB. FUS-GB digitally tracks the areas of lesions as well as trajectory and path of needle biopsies, enabling prior targets to be sampled and monitored. These benefits are not available in standard biopsy technique. An advantage of anatomical assessment of suspicious lesion size and the discriminative accuracy of detecting PCa with higher disease has been shown in Multi-parametric MRI (mp-MRI). The mp-MRI is also associated with histopathological stability allowing detection of tumor progression. A study by Von Beyme Cortés et al. also reported that the combined approach of FUS + TRUS-GB revealed more Gleason score

Figure 6: Bayesian prediction served in hierarchical summary receiver operating characteristic model by Rutter and Gatsonis for prediction of true sensitivity and specificity of (a) TRUS-guided biopsy; (b) magnetic resonance imaging + TRUS (fusion)-guided biopsy; (c) magnetic resonance imaging-guided biopsy; (d) contrast-enhanced ultrasound-guided biopsy
upgrades compared to FUS-GB alone although the result was not significant.

As for TRUS-GB, TPUS-GB, and CEUS-GB, they were ranked lower compared to others regarding four efficacy endpoints (PCa detection, clinically significant PCa detection, insignificant PCa detection, and HSROC). CEUS-GB provided a statistically significant improvement in discrimination between benign and malignant biopsy sites. CEUS-GB can better detect PCa by utilizing the characteristic of neoangiogenesis in PCa. It was shown that only tumor that has reached the size of 1 ml appears to have a high density of blood vessels, as smaller (<2 mm) tumors may be avascular. This may be the reason for nonvisualization of small tumors which lower the overall PCa detection. As for TPUS-GB, the limitations of TPUS-GB lay in its difficulties in visualizing hypoechoic areas thus may be the reason for low sensitivity rate.

In our review, we included 2109 patients undergoing prostate biopsy to analyze the complication and side effects related to procedure. Our results found that FUS-GB, MRI-GB, and FUS+TRUS-GB were more associated with less complication rate compared with TRUS-GB and TPUS-GB which had a higher risk for developing complications. MRI-GB was preferred because it is associated with lower pain intensity and fewer side effects. The samples which are taken are only from high suspicious areas on prior MRI. A fewer number of specimens are removed in a more directed technique based on prior MRI findings which eventually will reduce injury to surrounding structures. Fewer complications using FUS-GB were also reported in a study by Siddiqui et al. where they applied mp-MRI technology with ultrasound fusion-GB and confidently avoided side effects and complications, but at the same time, maintaining a high significant PCa detection rate.

Our results showed that the new biopsy techniques such as FUS-GB, MRI-GB, and FUS+TRUS-GB could result in a significantly higher rate for detecting PCa compared to random biopsy, translating to less biopsy related complications. This result leads us to believe that MRI-GB, FUS-GB, and FUS+TRUS-GB may become the first-line technique for detecting PCa in upcoming years.

There are several strengths of this review. First, the implementation of Bayesian framework in NMA as well as in HSROC model could provide better confidence in terms of decision-making results; therefore, it gives clarity for surgeons as well as patients for choosing the best strategy. Second, most of the studies included were RCTs, which permit a direct comparison between two diagnostic pathways with clinically relevant outcomes, as opposed to diagnostic cohort studies that can only inform us about test accuracy measures. Third, Regarding the suggestion from previous study, we managed to analyze complication rates in our study. However, a cost-effectiveness analysis was not performed in this study which would be a limitation.

**CONCLUSION**

This NMA and HSROC model showed that FUS+TRUS-GB, FUS-GB, and MRI-GB are superior to other biopsy strategies in diagnosing PCa with fewer complications. These results will assist in shared decision-making between patients, carers, and their surgeons.

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