Review – Prostate Cancer

Intraoperative Frozen Section for Margin Evaluation During Radical Prostatectomy: A Systematic Review

Eoin P. Dinneen a,b,*, Michelle Van Der Slot c, Kelvin Adasonla b, Jin Tan b, Jack Grierson d, Aiman Haider e, Alex Freeman e, Neil Oakley f, Greg Shaw a,b

a Division of Surgery and Interventional Science, University College London, Fitzrovia, London, UK; b Department of Urology, University College London Hospital, London, UK; c Department of Pathology and Urology, Aner Prostate Operation Clinic, Maasstad Hospital, Rotterdam, The Netherlands; d Surgical & Interventional Trials Unit, University College London, Fitzrovia, London, UK; e Department of Histopathology, University College Hospital London, London, UK; f Department of Urology, Sheffield Teaching Hospitals NHS Trust, Royal Hallamshire Hospital, Sheffield, UK

Abstract

Context: Surgical margin status and preservation of the neurovascular bundles (NVB) are important prognostic indicators for oncological and functional outcomes of patients undergoing radical prostatectomy (RP). Intraoperative frozen section (IFS) has been used to evaluate margin status during surgery with the intention of reducing positive surgical margins (PSMs) and guiding safe preservation of the NVBs during RP, but its value is controversial.

Objective: To evaluate current literature comparing outcomes of men undergoing RP with IFS versus RP without IFS.

Evidence acquisition: Medline, Embase, and Cochrane Library searches for all relevant publications (PROSPERO ID CRD42019125940), including comparative studies reporting on men undergoing RP with and without IFS, were performed. Outcomes of interest were surgical margin status, long-term oncological outcomes, NVB status, and erectile function (EF) recovery. Data were narratively synthesised in light of methodological and clinical heterogeneity of included studies.

Evidence synthesis: After screening 834 publications, 10 nonrandomised retrospective comparative studies (including 16,897 patients) were retrieved. The technique of IFS differed considerably between studies. Eight studies reported a reduction in PSM rates (−1.4% to −14.5%) with IFS, though two studies reported higher PSM rates (+0.4% and +10%) with IFS. Three studies reported on long-term oncological outcomes, and no difference was seen with IFS. Three studies reported on the performance of IFS systematically at the posterolateral margin of the prostate (neurovascular structure-adjacent frozen-section examination [NeuroSAFE technique]). In all these three studies, either NVB preservation or EF recovery was improved. All studies were deemed to be at either a serious or a moderate risk of bias.

Conclusions: No randomised controlled trials were identified, and significant heterogeneity existed with regard to many features of the studies included. Within the limitations of this review, the evidence suggests that IFS during RP can facilitate a modest reduction in PSM rates. There is evidence that IFS performed systematically at the posterolateral margin of the prostate can facilitate more NVB preservation. However, in the main, the lack of prospective, randomised, standardised research with long-term oncological and functional outcomes precludes strong conclusions and highlights the need for such studies.

* Corresponding author. Division of Surgery and Interventional Science, University College London, Charles Bell House, 43–45 Foley Street, London W1W 7TS, UK. Tel. 00447734976685.
E-mail address: eoin.dinneen@nhs.net (E.P. Dinneen).

https://doi.org/10.1016/j.euf.2019.11.009
2405-4569/© 2019 European Association of Urology. Published by Elsevier B.V. All rights reserved.
1. Introduction

Negative resection margins and neurovascular bundle (NVB) preservation during radical prostatectomy (RP) for prostate cancer (PC) are objectives predicting oncological and functional outcomes. Numerous studies have documented the negative impact of positive surgical margins (PSMs) on biochemical recurrence (BCR) in RP [1–3]. Conversely, it is now well recognised that preservation of NVBs by nerve sparing (NS) at RP confers improved postoperative potency and possibly continence [4–6]. The surgeon must plan the NS strategy by balancing the competing desires to maximise postoperative functional recovery and to avoid PSM.

The strategy employed is based on assimilation of data from several sources including multiparametric magnetic resonance imaging (mpMRI) [7], nomograms [8–10], digital rectal examination, and intraoperative desmoplastic tissue appearances [11] to predict extraprostatic extension (EPE) of PC. An alternative real-time technique to detect EPE of PC and adequacy of surgical resection is intraoperative frozen section (IFS) analysis of the prostate margin. IFS is performed with a view to secondary resection (SR) of the implicated corresponding peri-prostatic area if the IFS of the margin is positive. IFS during RP has been in the published medical literature for 20 yr now, but its value is still controversial [12,13]. The aim of the present study was to perform a systematic review of the literature exploring the role of IFS at RP.

2. Evidence acquisition

The systematic review protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42019125940).

2.1. Literature search

Our methods follow the principles outlined in the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) 2015 [14] statement and the Cochrane Handbook for Systematic Reviews of Interventions [15]. The Medline and Embase databases (using Ovid), and the Cochrane Library databases were systematically searched without date/language restrictions using subject headings and free text terms. The initial literature search was performed on 26 February 2019, and an updated search was performed on 18 September 2019. The search strategy is described in detail in the Supplementary material.

2.2. Eligibility

As proposed by the PRISMA guidelines, we used the Population, Intervention, Comparator, Outcome, and Study design model to direct eligibility. Studies were eligible if they included men undergoing RP (open, laparoscopic, and robotic) for PC (population), including IFS prostate margin evaluation (intervention), and were compared with men who did not have IFS during RP (comparator), to investigate the effects on oncological and functional outcomes (outcomes). Secondary publications, meeting abstracts, technical case reports, animal studies, and single-arm studies were excluded.

Following article identification and deduplication, two reviewers (E.D. and K.A.) independently screened all titles and abstracts. Full-text manuscripts of any titles/abstracts of relevance were obtained and assessed independently by the same two reviewers.

2.3. Data extraction

After full-text evaluation, data from eligible studies were independently extracted by two reviewers using a standardised predesigned data-extraction form. Discrepancies were resolved by consensus or with the involvement of a third reviewer (G.S.). To avoid overlapping of patient populations, if multiple publications reported on the same patient population, the largest study was included.

2.4. Risk of bias in individual studies

Two authors (E.D. and M.v.d.S.) independently assessed the risk of bias in each study for each included reported outcome separately, with disagreement settled by discussion as recommended [16]. The risk of bias evaluation was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions for including nonrandomised studies [17] and using the ROBINS-I tool (including a domain to assess the risk of confounding bias). A list of important potential confounders was developed a priori and included the following: selection of IFS according to surgeon decision or other discretionary features, stage, Gleason grade, and age.

2.5. Statistical analysis

The included studies were considered too heterogeneous in study design, patient population, and reporting of results to have results combined by a meta-analysis [18]. A narrative

Patient summary: The data of this review suggest that frozen section sampling of the prostate (ie, whilst the patient is still asleep) during prostate cancer surgery can reduce the likelihood of cancer being detected at the edge of the removed prostate. It also finds that a type of frozen section analysis (neurovascular structure-adjacent frozen-section examination [NeuroSAFE technique] can help allow the nerves around the prostate to be left intact safely during surgery. However, the studies in this review are very different from one another and generally at a high risk of errors. Therefore, comparisons and conclusions must be made carefully.
synthesis was performed instead (https://www.york.ac.uk/crd/guidance/). Inclusion of a small number of studies precluded statistical assessment of heterogeneity.

3. Evidence synthesis

3.1. Study selection

In total, 1266 records were identified from searches in electronic databases. After deduplication, 834 titles and abstracts were screened for eligibility (Fig. 1). Full publications of 45 references were ordered, and after screening, 10 studies were identified that met the inclusion criteria [19–28].

3.2. Quality of the studies

The quality of the 10 studies is demonstrated in the Supplementary material (Risk of bias table). All studies had a retrospective design, were carried out using resources from their home institution without conflicts of interest, and were performed without blinding of participants, personnel, or outcome assessment (though the authors felt that the lack of blinding impacted only the reporting of subjective outcomes, ie, erectile function [EF] recovery). The individual risk of bias assessment for each outcome is reported in the corresponding subsections; however, overall, of the 22 outcomes included in evidence synthesis, 15 were deemed to be at a serious risk of bias and seven at a
Table 1 – Characteristics of eligible studies in the systematic review and their baseline characteristics.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Country</th>
<th>Recruitment period</th>
<th>No. of patients</th>
<th>Type of Surgery</th>
<th>Oncological outcomes</th>
<th>NVB status</th>
<th>EF recovery</th>
<th>Age</th>
<th>Preop PSA</th>
<th>RP Gleason (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cangiolo (1999) [19]</td>
<td>USA</td>
<td>1989–1997</td>
<td>142</td>
<td>Open</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>61.3</td>
<td>10.3</td>
<td>G6 3 + 4 4 + 3 G8</td>
</tr>
<tr>
<td>Tsuibo (2005) [20]</td>
<td>USA</td>
<td>1998–2002</td>
<td>760</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>58</td>
<td>7.32</td>
<td>g7 25 a 4 6 4.4</td>
</tr>
<tr>
<td>Lavery (2010) [21]</td>
<td>USA</td>
<td>2007–2009</td>
<td>970</td>
<td>RALP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>59.2</td>
<td>6 30</td>
<td>g7 64 6 6</td>
</tr>
<tr>
<td>Heinrich (2010) [22]</td>
<td>Germany</td>
<td>2004–2006</td>
<td>287</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>58.6</td>
<td>7.15</td>
<td>g7 29 a 4 20</td>
</tr>
<tr>
<td>Schollm (2012) [23]</td>
<td>Germany</td>
<td>2002–2011</td>
<td>11 069</td>
<td>(10 427), RALP (642)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>4 10 211 55 17.7 5.8</td>
<td></td>
</tr>
<tr>
<td>Kakuichi (2013) [24]</td>
<td>USA</td>
<td>2004–2011</td>
<td>2608</td>
<td>RALP</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>60.7</td>
<td>6.6</td>
<td>g7 48.5 6 6.4</td>
</tr>
<tr>
<td>Petralia (2015) [25]</td>
<td>Italy</td>
<td>2010–2012</td>
<td>268</td>
<td>RALP</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>61.3</td>
<td>7.32</td>
<td>g7 56.7 6 11</td>
</tr>
<tr>
<td>Obej (2018) [26]</td>
<td>Turkey</td>
<td>2014–2016</td>
<td>170</td>
<td>RALP</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>61.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mirmilstein (2018)</td>
<td>UK</td>
<td>2008–2017</td>
<td>277</td>
<td>RALP</td>
<td>Yes</td>
<td>No a</td>
<td>Yes</td>
<td>58.1</td>
<td>7.309</td>
<td>50.2 9 5.8</td>
</tr>
</tbody>
</table>

EF = erectile function; IFS = intraoperative frozen section; NA = not available; NeuroSAFE = neurovascular structure-adjacent frozen-section examination; NVB = neurovascular bundle; PSA = prostate-specific antigen; RALP = robot-assisted laparoscopic prostatectomy; RP = radical prostatectomy.

a NVB status results are presented for before and after the introduction of the NeuroSAFE technique to their hospital, but not according to whether IFS/NeuroSAFE was performed.

moderate risk of bias. This indicates the largely poor quality of evidence synthesised in this review.

3.3. Study details

The 10 studies included a total of 16 897 patients; 7714 (45.8%) men had RP with IFS and 9183 (54.2%) had RP without IFS (Table 1). All but two studies [19-20] were published after 2010. Four of the studies were from the USA and the remaining six were from Europe (three from Germany, and one each from Turkey, Italy, and the UK). All were single-site studies. Five studies included men who had robot-assisted laparoscopic prostatectomy (RALP) only, three studies included open surgery only, and two studies included both RALP and open RP. In total, 5155 patients had RALP and 11 742 had open RP. Final pathological stage by study and according to the IFS or non-IFS group can be seen in Table 2. Overall, a total of 12 054 men (71%) had organ-confined disease on final histological diagnosis.

3.4. Baseline characteristics

Baseline characteristics of included patients are summarised in Table 1 (more details according to RP with IFS or without IFS are provided in Supplementary Table 1). The average age was similar across all studies, though two studies found that patients in whom IFS was performed were statistically significantly younger than those in whom IFS was not performed (Kakuichi et al [24] study; 59.5 vs 61.1 yr old, and Mirmilstein et al [27] study; 58 vs 62 yr old).

Pathological stage did not vary significantly between studies (see Table 2). Within studies however, four studies present statistically significant differences between stages within their respective groups. Kakuichi et al [24],

Table 2 – Final pathological stage of PC (pT).

<table>
<thead>
<tr>
<th></th>
<th>Overall (%)</th>
<th>IFS (%)</th>
<th>Non-IFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pT2</td>
<td>pT3a</td>
<td>pT3b</td>
</tr>
<tr>
<td>Cangiolo [19]</td>
<td>T1 + 2</td>
<td>38 (54)</td>
<td>59 (46)</td>
</tr>
<tr>
<td>Tsuibo [20]</td>
<td>T2 = 64</td>
<td>77 (15)</td>
<td>32 (4)</td>
</tr>
<tr>
<td>Lavery [21]</td>
<td>791 (81)</td>
<td>179 (19)</td>
<td>179 (19)</td>
</tr>
<tr>
<td>Heinrich [22]</td>
<td>245 (85)</td>
<td>42 (15)</td>
<td>111 (85)</td>
</tr>
<tr>
<td>Schollm [23]</td>
<td>7750 (70)</td>
<td>2164 (20)</td>
<td>1098 (10)</td>
</tr>
<tr>
<td>Kakuichi [24]</td>
<td>1889 (72)</td>
<td>564 (22)</td>
<td>151 (6)</td>
</tr>
<tr>
<td>Petralia [25]</td>
<td>141 (53)</td>
<td>106 (40)</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Obej [26]</td>
<td>111 (65)</td>
<td>45 (26)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Mirmilstein [27]</td>
<td>232 (84)</td>
<td>38 (14)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Preisser [28]</td>
<td>208 (60)</td>
<td>138 (40)</td>
<td>105 (67)</td>
</tr>
</tbody>
</table>

Overall = 12 054 (71%); 3486 (22%) = 11 054 (66%); 582 (4%) = 76 (11%); 762 (4%) = 0.2%

a Stage results given only as “T1/2” and “T3/4”.
b Final stage given as “confined to the prostate, extracapsular extension, and seminal vesicle invasion and note from authors, stage not mutually exclusive”.
c Stage classified only as pT2a-c and pT3a-b.
d Classified as “><” to pT3a.
e Classified as “><” to pT3.

For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.
Table 3 – Summary of IFS approach, margin status according to group, proportion of IFS positive, ability of secondary resection (SNR) to convert a PSA on IFS to an SNM on final RP analysis, and % of SNR tissue submitted positive for cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Site of IFS</th>
<th>IFS (n)</th>
<th>Non-IFS (n)</th>
<th>PSM rate IFS (%)</th>
<th>PSM rate non-IFS (%)</th>
<th>δ PSM rate (%)</th>
<th>% IFS positive</th>
<th>Ability to convert PSM IFS to SNM (%)</th>
<th>% SNR tissue + ve cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caegiano [19]</td>
<td>Posterolateral only when concern</td>
<td>48</td>
<td>94</td>
<td>24</td>
<td>22.4</td>
<td>+1.4</td>
<td>18.8</td>
<td>100</td>
<td>NA</td>
</tr>
<tr>
<td>Tsuboi [20]</td>
<td>Area of concern by surgeon</td>
<td>259</td>
<td>501</td>
<td>21</td>
<td>10</td>
<td>+11</td>
<td>8.9</td>
<td>73</td>
<td>16</td>
</tr>
<tr>
<td>Lavery [21]</td>
<td>“Visual concern” by surgeon</td>
<td>177</td>
<td>793</td>
<td>7</td>
<td>18</td>
<td>–11</td>
<td>6</td>
<td>54.5</td>
<td>NA</td>
</tr>
<tr>
<td>Heinrich [22]</td>
<td>Posterolateral only when concern</td>
<td>130</td>
<td>157</td>
<td>15</td>
<td>15.3</td>
<td>–12.2</td>
<td>6.9</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>Schlomm [23a]</td>
<td>Posterolateral NVB surface [2, d]</td>
<td>2567</td>
<td>2567</td>
<td>15</td>
<td>21.7</td>
<td>–6.5</td>
<td>27.2</td>
<td>86.2</td>
<td>23</td>
</tr>
<tr>
<td>Kakuchi [24]</td>
<td>Surgeon discretion</td>
<td>1128</td>
<td>1480</td>
<td>9.7</td>
<td>11</td>
<td>–13</td>
<td>5.3</td>
<td>63</td>
<td>NA</td>
</tr>
<tr>
<td>Petralia [25]</td>
<td>MRI-guided ECE concern</td>
<td>134</td>
<td>134</td>
<td>7.5</td>
<td>18.7</td>
<td>–11.2</td>
<td>17.4</td>
<td>72.2</td>
<td>NA</td>
</tr>
<tr>
<td>Obek [26]</td>
<td>Entire prostate margin [26] a</td>
<td>170</td>
<td>NA</td>
<td>8</td>
<td>22.5</td>
<td>–14.5</td>
<td>33</td>
<td>85</td>
<td>37</td>
</tr>
<tr>
<td>Mirmilstein [27]</td>
<td>Posterolateral NVB surface [2, d]</td>
<td>120</td>
<td>157</td>
<td>9.2</td>
<td>17.8</td>
<td>–8.6</td>
<td>14.5</td>
<td>NA</td>
<td>42.4</td>
</tr>
<tr>
<td>Preisser [28]</td>
<td>Posterolateral NVB surface [2, d]</td>
<td>156</td>
<td>190</td>
<td>15.4</td>
<td>29.5</td>
<td>–14.1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

ECE = extracapsular extension; IFS = intraoperative frozen section; MRI = magnetic resonance imaging; NVB = neurovascular bundle; PSM = positive surgical margin; PSN = pelvic side wall; RP = radical prostatectomy.

* Combined from 5.7% in non-IFS planned NS RP group and 17.2% in preplanned non-NS (non-IFS) RP group.
* Analysis of propensity score–matched cohort only.
* Studies performing IFS as per the NeuroSAFE description.
* Denotes IFS application where performed systematically to an area in all men in the IFS group, as opposed to on an ad lib basis.
* 3.5% atypical on IFS (10 of these 39 patients were shown to have cancer on the final analysis).

Mirmilstein et al [27], and Schlomm et al [23] performed RP with IFS in more patients with stage pT3a disease and fewer with pT2 disease than the non-IFS comparison group. This would suggest higher-risk disease in the IFS arm and potentially represent confounding that would bias in favour of the non-IFS group. Conversely, Preisser et al [28] performed RP with IFS in fewer patients with > pT3 disease than the group receiving RP without IFS (32.7% vs 45.8%, p = 0.02). This would likely result in confounding in favour of the IFS group. With regard to Gleason grade score, there is some heterogeneity between the studies included in this review as can be seen in Table 1. Only three studies report statistically significant differences in Gleason grade between IFS group and non-IFS groups. Mirmilstein et al [27], Schlomm et al [23], and Preisser et al [28] noted higher grade in the IFS versus non-IFS group, also confounding that would bias in favour of the non-IFS group. Schlomm et al [23] controlled for confounding by using propensity score matching for preoperative prostate-specific antigen, pT stage, Gleason score, and pN status.

3.5. IFS: site and technique

The area(s) of the prostate margin submitted for IFS evaluation varied considerably (see Table 3). Six studies reported IFS directed to evaluate areas perceived to be of concern for PSM or EPE anywhere on the prostate. This was deemed to be a significant source of confounding as a preintervention variable increasing the likelihood of PSM and known associated negative oncological outcomes in the IFS groups. Of these six studies where IFS was directed on a seemingly ad lib (as opposed to systematic application of IFS to all men) basis, the area of concern was directed by the operating surgeon in five studies [19–22,24] and by preoperative mpMRI in one study [25] (see Table 3). Obek et al [26] report a technique (Istanbul preserve) wherein almost the entire prostate margin is systematically sampled and submitted for IFS evaluation. In five studies, the posterolateral (NVB adjacent) margin was submitted only for IFS. In two of these studies, IFS was performed only at the posterolateral aspect when there was a suspicion of risk for EPE or PSM [19,22]. In the remaining three studies, evaluation of the posterolateral margin was performed systematically regardless of surgeon suspicion during RP. This systematic application of IFS at the posterolateral margins is called the neurovascular structure-adjacent frozen-section examination (NeuroSAFE) technique (see Fig. 2) [23,27,28].

Assessment of the quality of technical description of each study’s IFS approach is given in the Supplementary material. Furthermore, information pertaining to sensitivity and specificity (where given by authors) according to reference test (permanent histology) is provided in the Supplementary material.

3.6. Outcomes

We include an analysis of five outcomes of interest of RP influenced by the performance of IFS. These are PSM rates (and more detailed histological analysis), additional time for procedure, oncological outcomes (adjuvant therapies and BCR), NVB preservation during RP, and EF recovery. All 10 studies reported on PSM rates, four on oncological outcomes, six on NVB preservation, and three on EF recovery.

4. Results

4.1. PSM and histological analysis

Ten studies, including 11,052 patients, report on the effect of IFS on PSM rates (Table 3). The risk of bias was serious in six and moderate in four studies (see the Supplementary material, Risk of bias table). Eight studies report a reduction and
two report an increase in PSM rate with IFS (range −14.5% to +11%, median −9.8%). The largest reduction in the rate of PSM, −14.5%, was demonstrated by Obek et al [26] who describe the “Istanbul preserve”, which involves submitting large sections of the surface for IFS.

Two studies noted an increase in PSM rate with IFS, though both were deemed to be at a high risk of confounding in favour of the non-IFS group. Cangiano et al [19] found a 0.4% increase in PSM rates in their IFS group; however, the patients were allocated to IFS according to the suspicion of EPE or high-risk disease, and the authors also reported a higher proportion of pT3/4 disease in their IFS group compared with the non-IFS group (48% vs 39%). Tsutomi et al [20] found an 11% increase in PSM in their IFS group; however, IFS was performed in cases where the surgeon felt that there was a high risk of PSM and EPE after inspecting the prostate.

Conversely, the three other groups that reported performing IFS on prostate margin according to surgeon suspicion for EPE or PSM noted a reduction in PSM rates of 11%, 12.2%, and 1.3% (in the studies by Laverty et al [21], Heinrich et al [22], and Kakiuchi et al [24], respectively). Interestingly, Petralia et al [25] report an 11.3% reduction in PSM when the site submitted for IFS was selected according to the preoperative MRI report. They report a high proportion of IFS tissue submitted being positive for cancer (17.4%), as well as good sensitivity (78%) for the detection of PSM using their approach to IFS and an 11.2% improvement in the proportion of men with PSM in the IFS group. Although they did not detail how areas submitted for IFS were selected using MRI, this is an area of some promise as MRI becomes increasingly widespread prior to RP.

Of the three studies reporting on systematic IFS at the posterolateral NVB-adjacent surface (NeuroSAFE), all report a reduction in PSM rate: by 6.5%, 8.6%, and 14.1% in the studies of Schlomme et al [23], Mirmilstein et al [27], and Preisser et al [28], respectively.

Five studies included information on the presence of PC in the final histological analysis of the tissue submitted following SR when IFS was positive. Detection rates of cancer in SR specimens were low (range: 0–42.4%; see Table 3). This may reflect the facts that the cancer seen at the positive margin may indeed be the limit of the tumour, PSM does not necessarily denote EPE, and only by resecting more tissue it is possible to know what has been left behind, and it also highlights the complexity of identifying the correct area for SR when IFS is positive. Details pertaining to sensitivity and specificity between IFS and final margin status, and additional time/cost needed for IFS during RP (where reported by the authors) are presented and discussed as part of the Supplementary material.

4.2. Oncological outcomes

Four studies including the analysis of 6381 patients report on oncological outcomes in both IFS and non-IFS groups (see Table 4). Of the four studies, three were at a serious risk of bias [19,21,27] and one [23] had a moderate risk of bias. Schlomme et al [23] reported 5-yr BCR-free survival on propensity score–matched pairs from their series including 11 069 patients. Compared by pathological stage, BCR-free survival did not differ significantly according to whether IFS is performed or not: 85.4% versus 87.7% in pT2, 62.7% versus 63.6% in pT3a, and 34.6% versus 32.9% in pT3b. Mirmilstein et al [27] also report on the oncological outcomes of the NeuroSAFE technique, though the duration of follow-up is not as long and differs according to groups. They found BCR rates of 1.7% and 1.9% over an average of 15.4 and 31.4 mo in the IFS and non-IFS groups, respectively. Rates of adjuvant therapy given differed, with 5.7% of the IFS group and 1% of the non-IFS group receiving further treatment, though, given small numbers, this was not statistically significant. Additionally, the IFS group in their study had a significantly higher proportion of high-grade and high-risk PC than the non-IFS cohort. Laverty et al [21] report BCR at 5% in both groups but do not give the duration of follow-up. Cangiano et al [19] report that BCR was seen in five (all of whom had a
### Table 4 – Summary of oncolgical outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>IFS (n)</th>
<th>Non-IFS (n)</th>
<th>Follow-up duration (mean)</th>
<th>BCR IFS</th>
<th>BCR non-IFS</th>
<th>Adjuvant therapy IFS</th>
<th>Adjuvant therapy non-IFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lavery [21]</td>
<td>177</td>
<td>793</td>
<td>NA</td>
<td>5%</td>
<td>5%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Schlomm [23]a</td>
<td>2567</td>
<td>2567</td>
<td>BCR at 5 yr Adjuvant therapy follow-up NA</td>
<td>pT2 14.6%</td>
<td>pT2 12.3%</td>
<td>3.2%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Mirmilstein [27]</td>
<td>120</td>
<td>157</td>
<td>IFS 15.4 mo Non-IFS 31.4 mo</td>
<td>1.70%</td>
<td>1.90%</td>
<td>5.80%</td>
<td>1.90%</td>
</tr>
</tbody>
</table>

BCR = biochemical recurrence; IFS = intraoperative frozen section; NA = not available.

a Analysis limited to propensity score–match cohort.

### Table 5 – NVB status during RP.

<table>
<thead>
<tr>
<th>Study</th>
<th>IFS (n)</th>
<th>Non-IFS (n)</th>
<th>IFS (%)</th>
<th>Non-IFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Bilateral</td>
<td>Unilateral</td>
<td>Nil</td>
</tr>
<tr>
<td>Cangiano [19]</td>
<td>NA</td>
<td>82</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Lavery [21]</td>
<td>177</td>
<td>793</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Schlomm [23]a</td>
<td>2567</td>
<td>2567</td>
<td>96.6</td>
<td>63.3</td>
</tr>
<tr>
<td>Petralia [25]</td>
<td>134</td>
<td>134</td>
<td>NA</td>
<td>60</td>
</tr>
<tr>
<td>Obek [26]</td>
<td>170</td>
<td>NA</td>
<td>92.40</td>
<td>NA</td>
</tr>
<tr>
<td>Preisser [28]</td>
<td>156</td>
<td>190</td>
<td>95.50</td>
<td>85.30</td>
</tr>
</tbody>
</table>

IFS = intraoperative frozen section; NA = not available; NVB = neurovascular bundle; RP = radical prostatectomy.
a Analysis limited to propensity score–match cohort.

negative surgical margin (NSM) of 48 patients in the IFS group after a mean follow-up of 31 mo. There was no BCR in the nine patients who had positive IFS and underwent SR of the ipsilateral NVB. However, the authors do not report on oncological outcomes in the non-IFS group; therefore, these data are not included in Table 3.

### 4.3. NVB preservation

Six studies including 7030 patients report on NVB preservation with and without IFS. Of these six studies, three [23,25,28] had moderate and three [19,21,26] serious risk of bias. All studies report increased preservation of NVB during RP with IFS (Table 5). Three studies performed IFS away from the NVB–adjacent posterolateral prostate margin. These report a more modest increase in NVB preservation: 5% by Lavery et al [21], 4% by Petralia et al [25], and 4.9% by Obek et al [26]. Cangiano et al [19] report an increase in bilateral NVB preservation from 51.1% to 82% when IFS was used at the posterolateral margin of the prostate, when there was a suspicion of EPE. Two studies report on the NeuroSAFE technique and observe a pronounced increase in NVB preservation from 80.6% to 96.6% in Schlomm et al [23]’s propensity score–match paired cohort analysis and from 55.3% to 95.5% in the study of Preisser et al [28].

### 4.4. EF recovery

Only three studies including an analysis of 1389 patients report on EF recovery in men undergoing RP with and without IFS (Table 6) [19,21,27]. All three studies are deemed to be at a serious risk of bias. Mirmilstein et al [27] report the biggest improvement in EF recovery (NeuroSAFE technique). They defined potency as the ability to have penetrative sexual intercourse with or without the assistance of oral medications at 12 mo after surgery. This subjective assessment was collected by clinicians who were not blinded to whether the patient underwent IFS. At 12 mo, 77.3% of men in the IFS group were potent versus 50.9% in the non-IFS group. Lavery et al [21] report a 5% increase in NVB preservation as seen above. They also report a slightly improved EF recovery rate at 12 mo from 80% in the non-IFS group to 86% in the IFS group, though this does not feature prominently in their conclusions. Cangiano et al [19] also found that potency and partial potency (subjectively assessed by the interviewing physician) were improved in the group having IFS (36%) compared with an
alternative group not having IFS (13%), and were equivalent to those in a planned bilateral NS group (40%); however, the numbers in this study from 1999 are small.

4.5. Additional time and cost of IFS

Of the 10 studies, four [21,23,26,27] give additional information pertaining to the cost or additional time spent in the operating room in order to perform IFS during RP. Six other studies do not report on this parameter. Schlemm et al [23] report that the surgeon uses the additional time for IFS to perform the Rocco stitch, urethra-vesical anastomosis, and lymph node dissection; therefore, no additional time is spent under general anaesthesia when the NeuroSAFE technique is performed. Obek et al [26] report that patients undergoing IFS spent an additional 57 min (range 45–69 min) in the operating room. Laverty et al [21] outline costing of £229 per patient for IFS. Similarly, Mirmilstein et al [27] in the NHS setting report £550 additional expense per NeuroSAFE IFS case.

5. Discussion

Patients with localised PC do better after RP if they have NSM and preservation of the NVBs [1,6]. IFS margin evaluation is the standard practice in many tumour entities, but is controversial in RP. We report the first systematic review of the literature to use a transparent and rigorous methodology to compare outcomes after RP with and without IFS.

5.1. Margin status and IFS

Eight of 10 studies in this review find that the performance of IFS during RP reduced PSM rates. The overall range of differences was from a decrease of 14.7% to an increase of 11%. These widely differing rates of impact on PSM reflect several factors: (1) different IFS application sites, technical methods, and standards; (2) divergent characteristics of the surgery and patient selection across studies; and (3) different definitions (or likely different definitions when information was not given) of PSM. Moreover, all studies were deemed to be at a serious or moderate risk of bias. The most prominent confounder was the use of discretion to select patients who should have IFS. With regard to PSM rates, this likely biased results in favour of RP without IFS. Nonetheless, eight of 10 studies find that IFS reduced the rates of PSM.

5.2. Oncological outcomes

There is a paucity of comparative evidence about oncological outcomes following RP with and without IFS. Three of the four studies that include oncological outcomes in this review also report a reduction in PSM rates in the IFS group, but no difference was seen in BCR or adjuvant therapies. However, small cohort size and short follow-up may limit this interpretation in three studies [19,21,27]. Schlemm et al [23] (the largest and the best conducted study in this review) report no difference in oncological outcomes, which is of note given that they achieved significantly higher NVB preservation rates in the IFS group.

5.3. NVB preservation and EF recovery

Our review shows that systematic sampling of the posterolateral NVB-adjacent prostate margin (NeuroSAFE technique) in order to navigate NVB preservation is a potentially beneficial application of IFS. Both Schlemm et al [23] and Preisser et al [28] report markedly improved rates of NVB preservation following the introduction of the NeuroSAFE technique. However, without EF recovery or other functional outcomes, these results may be of limited value to patients. Mirmilstein et al [27] using the same technique demonstrate an improvement in EF recovery from 50.9% to 77.3% at 12 mo follow-up in men who were preoperatively potent. Our group is currently conducting a randomised controlled trial (RCT) to evaluate the same IFS technique, and will report on oncological and functional outcomes [29].

5.4. Limitations

High-powered RCTs on IFS are difficult to conduct as they require additional funding and ethical permissions. Additionally, centres routinely using IFS during RP may have lost equipoise and thereby find themselves unable to perform an RCT. The use of retrospective comparative studies is the next best approach, but interpretation of these results is threatened by allocation of patients to IFS or non-IFS RP that differs systematically.

Risk of bias analysis demonstrated that of the 10 studies and the 22 outcomes included in evidence synthesis, 15 outcomes were deemed to be at a serious risk of bias and seven outcomes at a moderate risk of bias. The risk of bias was predominantly due to the retrospective study design, confounding not controlled for, and selection bias. In six studies, patients in the IFS group were selected for IFS according to a feature suggestive of EPE, PSM, or aggressive cancer phenotype. This is a serious source of confounding. It is important, therefore, that certain outcomes heavily influenced by such confounders (PSM, BCR, and adjuvant therapy) are interpreted with caution [19–22,24,25].

Other limitations of this review pertain to heterogeneity between the included studies. The first is the lack of ability to control for the quality of RP using different surgical approaches and during different decades. Secondly, both frozen section and permanent pathology were performed by different pathologists. The different degrees of reporting in the manuscripts (see Supplementary Table 2) likely reflect divergent practices also, which may contribute to different results. Thirdly, we did not include single-arm case series of patients who had IFS RP, as the review was designed to include comparative studies only. Fourthly, only four of the studies include long-term functional or oncological outcomes, though these are the most important outcomes to patients. Although margin status and NVB preservation are important indicators of future recovery following RP, they do not represent patient experience, such as need for further adjuvant therapies. Fifthly, groups that do not identify benefit when
performing IFS during RP are less likely to be published (ie, publication bias). Sixthly, we cannot compare variables not consistently reported in individual studies such as surgeon volume, costs, and additional time required to perform IFS with RP. All these limitations introduce a bias as demonstrated in the risk of bias assessments, which lead us to infer that the conclusions made in this review are, at best, weak.

5.5. Comparison with current guidelines

Current guidelines do not recommend IFS during RP to reduce PSM rates [30,31]. The position of this guideline reflects the limitations of the quality of the evidence, as discussed above. Both American and European guidelines recognise that NS RP is associated with better EF recovery than non-NS RP. The European Association of Urology guidelines note that patients who are at a high risk of EPE, such as cT2c or cT3 PC or any International Society Uropathology PC grade >3 on biopsy, are a relative contraindication to NVB preservation. The guideline, however, notes that IFS (or externally validated nomograms and preoperative mpMRI) can help guide NS strategy. The inclusion of this recommendation in European guidelines is reflective of the higher quality of studies/evidence (as demonstrated in this review) presented by the groups performing the NeuroSAFE IFS RP technique.

6. Conclusions

This review has three main findings: (1) it highlights the poor level of evidence currently available and the difficulties comparing results from retrospective studies with different IFS strategies, and subsequent conclusions should bear these limitations in mind; (2) it suggests that IFS during RP may help achieve a modest reduction in PSM rates, though there is no evidence to conclude that this improves oncological outcomes; and (3) it suggests that systematic IFS sampling of the posterolateral aspect of the prostate margin (NeuroSAFE technique) can safely improve NVB preservation rates and EF recovery. Efforts should be made so that future research into IFS during RP will be standardised, comprehensively described, prospective, and randomised where possible. This would align with the advice for complex surgical innovations in the IDEAL recommendations [32]. The reporting of longer-term functional and oncological outcomes should also be prioritised in comparative studies as these are of utmost importance to patients.

Author contributions: Eoin P. Dinneen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dinneen, Van Der Slot, Grierson, Haider, Freeman, Oakley, Shaw.

Acquisition of data: Dinneen, Van Der Slot, Adasonla, Tan, Haider, Shaw.

Analysis and interpretation of data: Dinneen, Van Der Slot, Grierson, Haider, Freeman, Oakley, Shaw.

Drafting of the manuscript: Dinneen, Van Der Slot, Grierson, Oakley, Shaw.

Critical revision of the manuscript for important intellectual content: Dinneen, Van Der Slot, Grierson, Haider, Freeman, Oakley, Shaw.

Statistical analysis: Dinneen.

Obtaining funding: None.

Administrative, technical, or material support: Dinneen, Grierson.

Supervision: Freeman, Oakley, Shaw.

Other: None.

Financial disclosures: Eoin P. Dinneen certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Sponsor and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary material related to this article can be found in the online version, at doi:https://doi.org/10.1016/j.euf.2019.11.009.

References


For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.