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A systematic review: impact of in-office biopsy on safety and waiting times in head and neck cancer

A E Lim[1], A D G Rogers[1], M Owusu-Ayim[2], S Ranjan[2], J Manickavasagam[2,3] and J Montgomery[1]

[1]Department of Otolaryngology, Queen Elizabeth University Hospital, Glasgow, Scotland, [2]Department of Otolaryngology, Ninewells Hospital, Dundee, Scotland and [3]Tayside Academic Science Centre, University of Dundee, Scotland, UK

Main Article

Dr A Lim takes responsibility for the integrity of the content of the paper

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Author for correspondence:
Dr A Lim, Department of Otolaryngology, Queen Elizabeth University Hospital, 1345 Govan Rd, Glasgow G51 4TF, UK
E-mail: alison.lim@ggc.scot.nhs.uk

Abstract

Objective. This study aimed to assess the current literature on the safety and impact of in-office biopsy on cancer waiting times as well as review evidence regarding cost-efficacy and patient satisfaction.

Method. A search of Cinahl, Cochrane Library, Embase, Medline, Prospero, PubMed and Web of Science was conducted for papers relevant to this study. Included articles were quality assessed and critically appraised.

Results. Of 19 741 identified studies, 22 articles were included. Lower costs were consistently reported for in-office biopsy compared with operating room biopsy. Four complications requiring intervention were documented. In-office biopsy is highly tolerated, with a procedure abandonment rate of less than 1 per cent. When compared with operating room biopsy, it is associated with significantly reduced time-to-diagnosis and time-to-treatment initiation. It is linked to improved overall three-year survival.

Conclusion. In-office biopsy is a safe procedure that may help certain patients avoid general anaesthetic. It was shown to significantly reduce time-to-diagnosis and time-to-treatment initiation when compared with operating room biopsy. This may have important implications for oncological outcomes. In-office biopsy requires fewer resources and is likely to be cost-saving five-years following introduction. With high rates of sensitivity and specificity, in-office biopsy should be considered as the first-line procedure to achieve tissue diagnosis.

Introduction

Patients referred with two-week wait or urgent suspicion of cancer to head and neck cancer services are put through an urgent, fast-track system. The National Institute for Health and Clinical Excellence (NICE) advises that urgent suspicion of cancer referrals should be seen within two weeks of initial referral from their general practitioner.[1–3] The Scottish Government recommends that all patients referred via the urgent suspicion of cancer pathway should receive initial treatment within 62 days of receipt of referral, with a maximum of 31 days between initial diagnosis and start of treatment.[4]

With a growing incidence of head and neck cancer,[5] there has been increasing pressure on the urgent suspicion of cancer pathway and difficulty achieving Scottish Government targets. Guidelines suggest 95 per cent of urgent suspicion of cancer patients should be achieving the recommended targets, but in 2019, 84.4 per cent of urgent suspicion of cancer referrals received treatment within 62 days of referral.[6] In 2020, this increased to 92.8 per cent, but this improvement may be falsely reassuring because there was a 55 per cent decrease in the number of urgent suspicion of cancer head and neck referrals following the coronavirus 2019 (Covid-19) pandemic.[7]

The traditional assessment pathway for an urgent suspicion of cancer patient involves an out-patient clinic appointment with flexible transnasal endoscopy, followed by imaging and panendoscopy in the operating theatre under general anaesthetic or an operating room biopsy. Any areas that are suspicious for malignancy are biopsied intra-operatively to gain histopathological diagnosis. After imaging and biopsy are completed, the patient is referred to the multidisciplinary team (MDT), where the patient is staged using the tumour–node–metastasis classification, and the team discusses management options and treatment intent.

In-office biopsy of suspicious lesions is an alternative technique used to take histopathological samples. In-office biopsy can be carried out during the initial out-patient clinic consultation, without requiring operating room resources. In-office biopsy is effective in detecting head and neck cancer, with a sensitivity rate of 77.8 per cent and specificity rate of 95.1 per cent.[8] Patients with diagnosis at in-office biopsy can be referred directly to the MDT without waiting for an operating theatre space, and this may have a subsequent impact on cancer pathway times.[9]

The aim of this systematic review was to assess the current evidence on the safety and impact of in-office biopsy on cancer waiting times. We will also review evidence about cost-efficacy and patient satisfaction for in-office biopsy.

Materials and methods

A literature search was conducted in December 2020 by the authors and the National Health Service (NHS) Library Service. The databases included were: Cinahl, Cochrane Library, EmBase, Medline, Prospero, PubMed and Web of Science. The search was filtered to only include articles published from 2010 to 2020 and in the English language. The search strategy (Appendix 1) was used and adjusted for each database. The results were exported to EndNote™ reference management software and duplicates were removed. Ethical permission was not required as no original research was conducted.

Inclusion and exclusion criteria were created and used in the review of the results. The authors included articles about adult patients (over 16 years old) and patients who had undergone endoscopic biopsy for a malignancy of the head and neck. Articles were excluded if the biopsies were conducted for benign conditions or oral malignancies and if the article did not contain original data (e.g. commentaries, correspondence, single case reports). Two authors carried out independent title and abstract reviews of the search results following Preferred Reporting Items of Systematic Reviews and Meta-Analyses (guidance, flow diagram shown in Appendix 2).[10]

Results

There were 19 741 search results from the literature search. Two additional papers that were not identified from our literature search were found from reading around the literature and added to the list of titles. Search results were uploaded to EndNote and duplicates were removed, leaving a total of 16 535 papers for title review. Two authors independently carried out title screening and excluded 16 437 papers. Any disagreements were resolved through discussion and consensus. A total of 98 abstracts were independently screened, and from this 27 full articles were reviewed. A total of 22 articles were included in the final systematic review; these are summarised in Table 1.

Discussion

Safety

Tolerability

Tolerability is a key outcome measure for in-office biopsy. It has implications for adequate tissue acquisition and patient satisfaction. As defined by Lippert *et al.*, tolerability is 'the ability to obtain a piece of tissue for pathological analysis'.[18] Cohen and Benyamini demonstrated an association between poorly tolerated procedure and insufficient tissue sample for diagnosis.[15] Tolerability may be subject to individual operator skill and successful application of local anaesthesia. Other factors such as patient selection and biopsy subsite have been linked to tolerability. For example, Mohammed *et al.* highlighted that most procedures that were abandoned because of patient intolerance were biopsies for glottic lesions.[29] Lippert *et al.* also specify difficulty obtaining biopsies of the true vocal folds as well as the laryngeal surface of the epiglottis.[18]

Across the studies, only a very small proportion of patients did not tolerate the procedure as shown in Table 2. There were 23 cases of procedure abandonment because of poor tolerability in the 2272 patients considered (less than 1 per cent). More research may be beneficial to objectively assess tolerability, including standardisation of reporting. However, all studies were aligned, and demonstrated an overall high degree of tolerability associated with in-office biopsy.

Complications

Complications of in-office biopsy are of significant interest because patient safety is paramount. Any concern regarding risk of airway-threatening events is likely to limit where in-office biopsy can be safely performed and therefore limit its utility. Table 3 summarises the papers that included comment on complications. Thirteen studies report none. Most complications reported were minor, self-limiting and required no intervention. Only Wellenstein *et al.*[22] reported serious complications requiring intervention. Most significantly, there was one case of laryngeal oedema, in the context of a large, bilateral, glottic mass, which required intervention in the form of urgent tracheostomy scheduled the following day.

Other complications requiring management included anterior epistaxis requiring topical 0.1 per cent xylometazoline to arrest, and laryngeal bleeding following injection of topical anaesthesia through the cricothyroid membrane. This was managed by subcutaneous injection of adrenaline around the cricothyroid membrane. One patient suffered post-procedure dizziness and hypotension which improved following administration of intravenous fluids.

The issue regarding whether in-office biopsy can be undertaken safely in patients on anticoagulation medicine is raised by three studies. Castillo-Farias *et al.*[16] discuss the disadvantage of in-office biopsy in terms of potential delayed time to diagnosis by the need to defer the procedure. In contrast, Wellenstein *et al.*[22] and Schutte *et al.*[24] did not require anticoagulation to be withheld prior to in-office biopsy. They report that no bleeding complications occurred. They conclude that anticoagulation medication is not a contraindication to in-office biopsy, which can still be safely performed. The authors do not provide details such as total numbers of anticoagulated patients undergoing in-office biopsy or information regarding specific subtypes of anticoagulation medication. Therefore, this would be an area of interest for further research.

The studies in these papers do not comment on complications associated with operating room biopsy, which, while being the current 'gold standard' for tissue diagnosis, is neither risk nor morbidity-free. In particular, patients with overt, advanced, airway-threatening head and neck malignancy may undergo a high-risk general anaesthetic for the purpose of tissue diagnosis. At least 1.6 per cent of patients undergoing panendoscopy require unplanned tracheostomy, and another proportion undergo planned local anaesthetic tracheostomy to secure the airway, potentially resulting in a lengthy hospital stay.[33] In many cases, after confirmation of the initial clinical diagnosis, the histopathology does not influence further management, which is best supportive care for 21 per cent of patients.[34]

The Lancet recently published an international consensus on the management of head and neck cancer in the setting of 'acute resource constraint', for example, as a consequence of the Covid-19 pandemic. In a situation whereby a healthcare

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Table 1. Summary of the papers included in the systematic review

First author	Year of publication	Study duration	Type of study	Level of evidence	Patients (*n*)	Mean age (years)	Age range (years)	Type of biopsy equipment
Naidu *et al.*[11]	2012	2006–2008	Retrospective	IV	12	62.5	–	Flexible digital videolaryngoscopy (ENF Olympus*)
Cohen *et al.*[12]	2013	May 2006 to January 2010	Prospective	IV	102	–	30–89	KayPentax† or ENT-2000 endoscope‡
Zalvan *et al.*[13]	2013	–	Retrospective	IV	26	62	20–86	Flexible scope KayPentax†
Pan *et al.*[14]	2013	April 2010 to December 2010	Retrospective	IV	19	50.5	37–63	Flexible laryngoscopy, narrow band imaging system ENF Olympus*
Cohen & Benyamini[15]	2014	–	Prospective	IV	117	66	30–89	Transnasal fibreoptic laryngoscopy Pentax-FNL-10 RP3†, Vision Sciences ENT-2000‡
Castillo- Farias *et al.*[16]	2015	April 2008 to December 2011; January 2012 to November 2012	Prospective	II	88	65	39–85	Channelled nasendoscope, Karl Storz**
Richard *et al.*[17]	2015	January 2010 to July 2013	Retrospective	IV	261	62	21–84	Distal chip video endoscope, ENT-5000, Vision Sciences‡
Lippert *et al.*[18]	2015	2007–2013	Retrospective	IV	116	–	–	Flexible distal chip laryngoscope, VNL-1570STK Pentax†
Fang *et al.*[19]	2015	May 2010 to April 2011	Retrospective	III	20	55.1	–	Flexible laryngoscopy with narrow band imaging, ENF type VT2, Olympus*
Cha *et al.*[20]	2016	–	Retrospective	IV	581	67	20–91	Flexible endoscope, ENF-VT, Olympus*
Chang *et al.*[21]	2016	January 2010 to February 2013	Prospective	IV	90	58	48–68	Flexible laryngoscopy, narrow band imaging-guided
Wellenstein *et al.*[22]	2017	April 2012 to April 2016	Retrospective	IV	187	66.8	43–92	Flexible endoscopic biopsy (VNL Pentax†)
Cohen *et al.*[8]	2018	–	Retrospective	IV	355	63.6	–	Flexible endoscope
Saga *et al.*[23]	2018	January 2006 to February 2016	Retrospective	IV	30	62.2	40–93	Videoendoscope, Olympus BF 240 and Olympus Evis Exera*
Schutte *et al.*[24]	2018	2010–2013	Prospective	II	188	65.9		Pentax flexible, video endoscope†
Lee *et al.*[25]	2018	January 2010 to January 2016	Retrospective case control	III	114	–	>18 years	–
Marcus *et al.*[26]	2019	January 2013 to August 2015	Retrospective cohort + financial analyses	III	48	–	Adult (>18 years)	Channeled, distal chip laryngoscope Pentax†
Wellenstein *et al.*[26]	2019	January to September 2016	Prospective	III	41	66.6	29–87	Transnasal oesophagoscope EE-1580K, Pentax Medical†
Hassan *et al.*[28]	2019	December 2013 to September 2015	Prospective	IV	43	39	28–52	Flexible laryngo-bronchoscope, Olympus*
Mohammed *et al.*[29]	2019	–	Retrospective case series	IV	134	65.8		Transnasal oesophagoscopy, Pentax†
Mozzanica *et al.*[30]	2020	January 2010 to January 2016	Prospective	IV	55	67	55–82	Flexible endoscope
Schutte *et al.*[31]	2020	2009 and 2014	Retrospective	III	486	64.8	–	–

*Olympus, Tokyo, Japan; †Pentax, Tokyo, Japan; ‡Vision Sciences, Orangeburg, New York; **Karl Storz, Tuttlingen, Germany

Table 2. Summary of papers discussing tolerability

Author & year	Patients (*n*)	Not-tolerated/abandoned procedures (*n*)
Cohen *et al.*[15] 2014	117	6
Naidu *et al.*[11] 2012	12	1
Mohammed *et al.*[29] 2019	134	14
Lippert *et al.*[18] 2015	116	2

institution is suffering severely reduced staffing and operating room and in-patient capacity, the consensus recommends that if a biopsy can be performed under local anaesthesia, no panendoscopy is required.[35] Given that in-office biopsy is sufficient to make a diagnosis in the context of potential harms because of resource constraint, one might also consider the potential avoidable harms, and ethics, of general anaesthesia in high-risk patients where in-office biopsy could provide the same diagnosis.

Cost analysis

Cost analysis of in-office biopsy versus operating room biopsy has been studied in a number of papers (see Table 4) seeking to calculate the potential savings associated with avoiding the operating room. There were eight studies that explored the cost efficacy of out-patient biopsy. Four of these studies were based in the USA or Taiwan and thus are limited in their transferability or relevance to the UK healthcare system. In particular, there is some variability in what costs were reported. Much of the financial analysis from the USA and Taiwan studies is centred on 'billable costs', 'opportunity costs' and 'reimbursement rates' by insurance companies. There is less discussion regarding the actual cost of the resources involved. Reimbursement rates tend to be based on the outcome of price negotiations between insurers and healthcare providers, taking into account the clinical and economical value of the treatment.[36] Therefore, they are not as reliable a surrogate of cost efficacy than an analysis based on actual hospital costs. Despite this, all studies evaluating cost agreed that in-office biopsy required fewer resources and was cheaper than operating room biopsy.

Four studies were of European provenance (Netherlands and Spain) and therefore of potentially increased applicability. The European studies suggested significant cost savings of between £658 and £1420 per patient undergoing in-office biopsy in lieu of operating room biopsy. One paper makes the point that even after accounting for negative biopsies requiring additional diagnostic procedures, including operating room biopsy, savings in this range were still possible.[24]

The cost analyses of Castillo-Farias *et al.*,[16] Saga *et al.*[23] and Schutte *et al.*[24] were limited by the absence of actual financial data collected. Instead, they provided projections of savings based on data generated from estimated resource costs. In comparison, Wellenstein *et al.*[26] was a prospective cost analysis study with the aim of investigating the feasibility of office-based biopsy. It collected costs based on actual resources used in the assessment of 41 patients, accounting for any unexpected variation. The results of this higher quality study supported the findings of the earlier work performed in this area, highlighting savings of up to €831 (£720) per procedure.

Despite a relative lack of standardisation and robust methodology across the studies looking at cost, in-office biopsy is consistently found to be cheaper and less resource intense than operating room biopsy. This remains constant across a variety of healthcare systems in different parts of the world.

Table 3. Summary of papers discussing complications

Author & year	Patients (*n*)	Complications
Cohen *et al.*,[15] 2014	117	2 × epistaxis, 1 aspiration
Cohen *et al.*,[8] 2018	355	2 × epistaxis, 1 vocal fold haematoma, 1 aspiration
Chang *et al.*,[21] 2016	90	1 vasovagal reaction*
Wellenstein *et al.*,[22] 2017	187	1 epistaxis*, 1 laryngeal bleeding*, 1 laryngeal oedema*, 1 laryngospasm (self-limiting)
Hassan *et al.*,[28] 2019	43	1 × post-procedure blood-tinged saliva and choking sensation
Wellenstein *et al.*,[26] 2019	41	2 × vasovagal reactions, 2 × epistaxis
Cha *et al.*,[20] 2016	581	No complications, no abandoned procedures
Richard *et al.*,[17] 2015	261	No complications, no abandoned procedures
Saga *et al.*,[23] 2018	30	No complications, no abandoned procedures
Pan *et al.*,[14] 2013	19	No complications, no abandoned procedures
Zalvan *et al.*,[13] 2013	26	No complications, no abandoned procedures
Fang *et al.*,[19] 2015	20	No complications, no abandoned procedures
Lee *et al.*,[25] 2018	44	No complications, no abandoned procedures
Mozzanica *et al.*,[30] 2020	55	No complications, no abandoned procedures
Castillo-Farias *et al.*,[16] 2015	88	No complications, no abandoned procedures
Schutte *et al.*,[24] 2018	53	No complications, no abandoned procedures
Naidu *et al.*,[11] 2012	12	No complications, no abandoned procedures
Lippert *et al.*,[18] 2015	116	No complications, no abandoned procedures
Mohammed *et al.*,[29] 2019	134	No complications, no abandoned procedures

*Intervention required

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Table 4. Summary of papers discussing cost analysis

Author & year	Country	In-office biopsy cost	Operating room biopsy cost	Savings per procedure per patient	In-office biopsy as percentage cost of operating room biopsy (%)
Naidu *et al.*,[11] 2012	USA	$2053.91 (£1482.43)	$9024.47 (£6513.51)	$6970.56 (£4984.89)	22.80
Marcus *et al.*,[26] 2019	USA	$7000 (£5003.18)	$11 000 (£7862.14)	$4000 (£2858.96)	63.60
Fang *et al.*,[18] 2015	Taiwan	NT$1264 (£32.58)	NT$10 913 (£281.32)	NT$9649 (£248.74)	11.60
Castillo-Farias *et al.*,[16] 2015	Spain	$65.44 (£47.23)	$1253.52 (£904.74)	$1188.08 (£853.04)	5.20
Saga *et al.*,[23] 2018	Spain	Data not provided	Data not provided	€1631 (£1420.20)	Data not provided
Schutte *et al.*,[24] 2018	Netherlands	€87.95 (£76.95)	€821.58 (£718.84)	€733.63 (£633.75)	10.7
Wellenstein *et al.*,[26] 2019	Netherlands	€583.54 (£507.65)	€1414.95 (£1232.07)	€831.41 (£720.12)	41.20

In 2018, The Scottish Health Technology Group published a budget impact analysis of in-office biopsy versus operating room biopsy from an NHS Scotland perspective. They assessed that the initial investment cost of flexible endoscopic equipment could be offset by the savings made through in-office biopsy within a 5-year time period, and savings of £420 000 every year thenceforth.[37] Higher quality, prospective cost analyses based on the UK healthcare system would be of particular value to evaluate the precise business case for in-office biopsy, although the authors do not believe this would challenge the trend highlighted by previous studies.

Waiting times

The National Institute for Health and Clinical Excellence and the Scottish Referral Guidelines for Suspected Cancer mandate that patients should expect a diagnosis of head and neck cancer within 31 days of referral and to commence treatment within 62 days.[4] Diagnosis and decisions regarding treatment can only be made following tissue acquisition and subsequent histopathological confirmation of cancer. Delays to diagnosis and treatment in head and neck cancer have been strongly associated with poorer outcomes including increased mortality. One particular study demonstrated a tumour-volume doubling time in head and neck cancer of 30 days for a cohort of patients with the most aggressive disease. They also demonstrated that 34 per cent of patients showed radiological progression of disease within 28 days.[34] Therefore, minimising avoidable delays is essential to optimising patient outcomes as well as compliance with these targets.

Four studies in our review produced complete data comparing time to diagnosis and time to treatment. The results were concordant in demonstrating reduced time to diagnosis associated with in-office biopsy (2.0–7.5 days) versus operating room biopsy (9.0–23.0 days). Three studies[17,24,31] also demonstrated reduced time to treatment for in-office biopsy (21.0–27.0 days) with respect to operating room biopsy (34.0–48.8 days).

In contrast, as seen in Table 5, Lee *et al.*[25] did not find any significant difference for time to treatment, despite observing a reduced time to diagnosis by 15.5 days with in-office biopsy. They account for the loss of this initial advantage of in-office biopsy by a combination of system factors and referral bias. In their practice, patients in the operating room biopsy arm can be discussed by the MDT if they have undergone fine needle aspiration positive biopsy without having had a confirmed primary tumour or having yet undergone panendoscopy. They also suggest delays associated with dental consultations and fitting for custom radiotherapy head and neck moulds as also potentially skewing the results.

Furthermore, it is important to note that in addition to in-office biopsy, Schutte *et al.*[31] also introduced combined MDT clinics at the initial consultation. These involved head and neck surgeons, oncology and other allied healthcare professionals. Although in-office biopsy was considered a main intervention for their 'optimised work-up program', their results should not be considered in a pure in-office biopsy versus operating room biopsy context.

Overall, in-office biopsy has been consistently shown to significantly reduce time to diagnosis. The majority of studies go further to demonstrate that this also leads to earlier initiation of treatment. With this evidence demonstrating that treatment can be initiated up to 26 days sooner and that disease progression and upstaging can occur in over a third of patients within 28 days, it is clear that in-office biopsy has great potential to expedite and improve oncological outcomes.[32] In fact, Schutte *et al.*[31] found 3-year overall survival to be 12 per cent higher in the cohort of patients that underwent in-office biopsy and commenced treatment on average 13 days sooner.

Clearly, this is a key area of interest and warrants further investigation and research. The argument linking in-office biopsy, reduced waiting times and improved survival would be strengthened by larger, more highly powered, prospective studies, with a narrow focus on in-office biopsy versus operating room biopsy while controlling for other variables.

Patient satisfaction

Standardised measurements of patient satisfaction have been infrequently published in the literature; it is more common for satisfaction to be informally reported. Mohammed *et al.*[29] studied 134 attempted transnasal oesophagoscopy biopsy procedures of the upper aerodigestive tract, most commonly of the glottis and tongue base. The authors commented that they were unable to carry out 19 of the attempted procedures and reported that 13 of these patients refused to have a further in-office biopsy and were subsequently referred for operating room biopsy. However, reasons for patient refusal or measurement of patient experience were not reported.

Table 6 shows the two papers from the systematic review that measured patient experience. Wellenstein *et al.*[26] used the visual analogue scale (VAS) to measure patient experience for 35 patients following in-office biopsy. The VAS asked

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Table 5. Summary of papers discussing patient waiting times

Author & year	Time to diagnosis (in-office biopsy) (days)	Time to diagnosis (operating room biopsy) (days)	Time to treatment initiation (in-office biopsy) (days)	Time to treatment initiation (operating room biopsy) (days)	Days saved by in-office biopsy to initiation of treatment (days)
Lee *et al.*,[25] 2018	7.5	23.0	49.6	51.7	2.1
Schutte *et al.*,[31] 2020	2.0	9.0	21	34	13
Schutte *et al.*,[24] 2018	2.0	16	27	41.5	14.5
Lippert *et al.*,[18] 2015	Data not provided	Data not provided	24.2	48.8	24.6
Cohen *et al.*,[8] 2018	10.7	3–4 weeks slower than in-office biopsy	Reduced	Data not provided	Data not provided

patients to rate their experience from 1 to 10, with 1 being the least unpleasant to 10 being the most unpleasant, and a mean score was calculated for each domain. Mean VAS score was 1.9 for nasal pain when inserting the endoscope and 1.7 for throat pain throughout the procedure. Patients were also asked to score on inconvenience because of gag reflex, nausea and burping, and mean scores were 1.5, 0.3 and 2.2, respectively. These results give an indication that patient experience of in-office biopsy is well tolerated.

Schutte *et al.*[31] compared patient experience in the conventional pathway with operating room biopsy against optimised pathway with in-office biopsy. A total of 139 patients were given a questionnaire, the Consumer Quality Index for Oncological Care, to rate their experience of the conventional or optimised pathways. Scores were significantly higher in the patients in the optimised pathway group. The introduction of the in-office biopsy in the optimised pathway may have contributed to the higher Consumer Quality Index scores, but satisfaction regarding in-office biopsy was not independently measured.

- In-office biopsy is safe, with most articles reporting only minor and self-limiting complications
- Patient tolerability of in-office biopsy was good, with a procedure abandonment rate of less than 1 per cent
- In-office biopsy is cost-effective, with all papers demonstrating a cost saving
- In-office biopsy improves treatment pathway times, with faster time to diagnosis and initiation of treatment
- There is little evidence on patient satisfaction of in-office biopsy compared with operating room biopsy
- In-office biopsy is an effective alternative to operating room biopsy and has a number of advantages

The literature lacks evidence regarding patient experience of in-office biopsy. The small number of quantitative questionnaire studies give an insight that patient experience of in-office biopsy is positive. Anecdotal comments on patient satisfaction can provide interest to the reader, but the literature needs further evidence of patient experience using standardised measurement.

Limitations

The main limitation of this systematic review was concerning the quality of evidence, and the fact that most of the primary articles included were retrospective cohort studies. This category of evidence is at risk of bias, particularly in patient selection and would be classified as lower in quality compared with randomised controlled trials. Patients in the cohort studies were also poorly matched with regards to factors such as biopsy site, specific type of equipment used and skill-level of the clinician performing the procedure. Discrepancies in these variables could affect the complication rate of in-office biopsy procedures.

Table 6. Papers discussing patient experience

Author & year	Measure of patient experience
Schutte *et al.*,[31] 2020	Consumer Quality Index for Oncological Care
Wellenstein *et al.*,[26] 2019	Visual analogue scale

Conclusion

This review of the literature has found in-office biopsy to be reported as a safe procedure, with very few serious complications documented in the current evidence. Moreover, it is well tolerated, with procedure abandonment occurring in fewer than 1 per cent of cases. Utilisation of in-office biopsy can lead to significantly faster times to diagnosis and treatment. This may have important implications for oncological outcomes and warrants further investigation. There is a lack of evidence about patient satisfaction comparing in-office biopsy versus operating room biopsy, and although initial results are positive, it remains an area of interest for further study. In-office biopsy has been consistently shown to be a highly cost-effective alternative to operating room biopsy across a variety of healthcare systems throughout the world.

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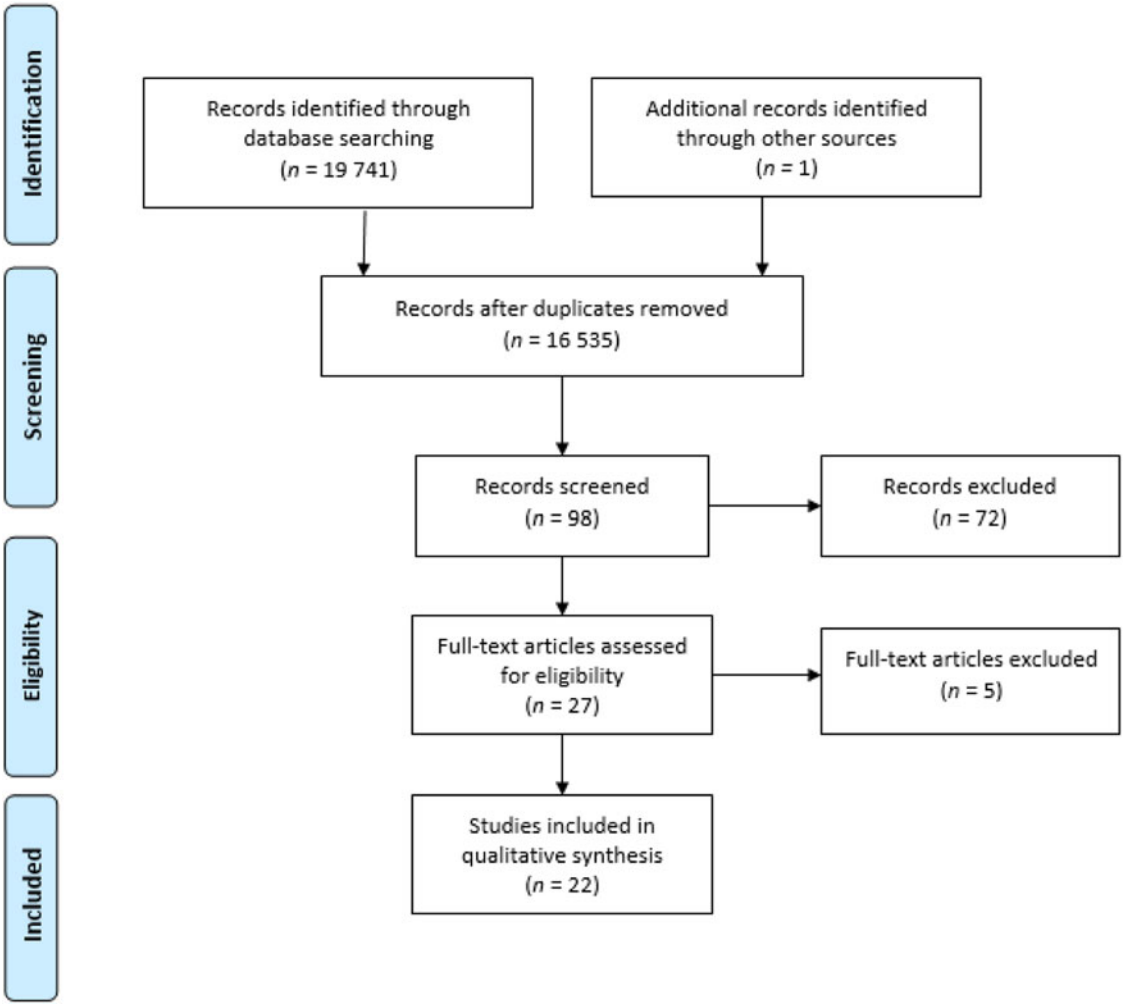
Appendix 1. Search strategy for systematic review

#	Search statement	Results
1	laryn* OR head and neck* OR vocal cord* OR pharyn* OR tongue base* OR nasopharyn* OR supraglottis* OR hypopharyn* OR oropharyn*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
2	outpatient* OR clinic* OR awake* OR local anaesthetic* OR office-based* OR in-office* OR office* OR fibreoptic* OR fibre-optic* OR fiberoptic OR fiber-optic* OR optical fibre* OR optical fiber*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
3	1 and 2	
4	biopsy* OR tissue biopsy* OR endoscopic biopsy*. OR flexible laryngoscopy* OR direct laryngoscopy* OR microlaryngoscopy* OR image guided* OR panendoscopy*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
5	cancer* OR tumour* OR malignancy* OR carcinoma* OR squamous cell carcinoma* OR dysplasia*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
6	4 or 5	
7	3 and 6	

Appendix 2. Preferred Reporting Items of Systematic Reviews and Meta-Analyses flow diagram



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