National Institute for Health and Care Excellence

IP51/3 Minimally invasive radical hysterectomy for early stage cervical cancer

IPAC dates: 16 January 2020 and 8 October 2020

There were 2 consultations for this guidance. The first ended in November 2019 and the second ran from 25 June 2020 to 23 July 2020.				
Consultation 1				
Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
1	Consultee 1 NHS Professional	**1.1**	These recommendation are bizarre. They contradict all the other organisations recommendations (ESGO, BGCS, NCCN, SERGS). It should be noted that the RCT is level 2 evidence not level 1. There is no evidence that a laparoscopic approach is of any harm for tumours of less than 2 cm and in the UK it is rare for the large tumours reported on in these studies to have surgery. Most large tumours receive chemoradiotherapy. I would recommend you read the editorials in JGO and IJGC	Thank you for your comment. Consultee disagrees with main recommendation. The main recommendation was changed.
2	Consultee 2 British Gynaecological Cancer Society	**1.1**	We welcome the publication of NICE guidance in this important area. We thank NICE for an opportunity to act as stakeholders in this consultation and submit our response below. The British Gynaecological Cancer Society (BGCS) is the professional home of health providers working and researching the area of gynaecological cancers. Our members consist of medical practitioners, clinical nurse specialists and other allied professionals, including scientists who have an interest in gynaecological cancers. We represent trainees, nurses, unit leads, oncologists, pathologists and radiologists and have a total membership in excess of 400. The BGCS produces evidence-based guidelines for the management of gynaecological cancers that are peer reviewed through a panel of international	Thank you for your comment. Consultee agrees with main recommendation for women with cervical cancer >2 cm but suggests different recommendations for women with cervical cancer <2 cm. The main recommendation was changed.

			referees. BGCS Council members are also representatives of the European Society of Gynaecological Oncology and the International Gynaecological Cancer Society. As a society, we are committed to supporting our members deliver the highest standards of care for women with cervical cancer. The BGCS convened a working group to establish the society's position on the use of minimal access surgery for cervical cancer following publication of two important clinical papers from the United States: the LACC randomised controlled trial (Ramirez et al, NEJM 2018) and epidemiological SEER data analysis (Melamed et al, NEJM 2018); both of which demonstrated survival benefit for women who underwent surgery by the open route. The LACC study and additional retrospective data were carefully scrutinised to determine whether the move to open surgery for cervix cancer applies to all stages/dimensions of tumour (Stage 1a2-1b2 (FIGO 18)). Some of the retrospective data suggest a differentiation between tumours <2cm (stage 1a2 and 1b1 (FIGO 2018)) and tumours >2cm (stage 1b2 (FIGO 2018)). However, the LACC study was not powered to address the safety of minimally invasive surgery for women with tumours <2cm, indeed recurrences occurred in both the control and trial arm – 14% of recurrences in open surgery were <2cm compared with 19% in the minimally invasive surgery group. With these caveats, a post hoc subgroup analysis in the LACC trial did not find evidence of poorer survival outcomes in the group undergoing minimal access surgery. The BGCS has worked with the National Cancer Registration and Analysis Service (NCRAS) to undertake a review of outcomes for women with FIGO Stage 1 cervical cancer who underwent radical hysterectomy by the minimal access (either laparoscopic or robotic) or open (laparotomy) route during 2013 – 2016. Following this analysis, the BGCS working group produced a statement and lay summary dated May 2019 with agreement from NHS England, the RCOG and PHE prior to public release. The BGCS strongly advised	

			caution in offering minimal access surgery to women with cervical cancer and called for further analysis of NCRAS data to investigate whether adverse oncological outcomes were confined to women with larger tumours > 2cm, as suggested by the results of the LACC trial. Since publication of the BGCS statement, additional data on equivalent survival outcomes in women undergoing minimal access surgery across European centres for tumours < 2 cm has been presented at ESGO 2019, as well as from retrospective UK survival data for cervix cancer comparing open and minimally invasive surgery (Martin-Hirsch et al, BJOG 2019) ***Having reviewed the evidence carefully, the BGCS supports NICE recommendation to discontinue minimal access surgery to women with cervical cancer > 2cm. However,*** ***We urge NICE to be cognisant of the uncertainty of evidence with respect to women with cervical cancer < 2 cm.*** A ban on minimal access surgery for tumours < 2 cm would not be advisable, as we discuss below. 1) Women managed with conisation or simple hysterectomy alone for early stage cervical cancer Early stage cervix cancer (FIGO stage 1a1 to 1b2, FIGO 2018) is managed surgically in the majority of cases. The very earliest stage of cervix cancer (FIGO stage 1a1) is managed by local excision alone (cone biopsy or large loop excision of the transformation zone (LLETZ)). There is no additional oncological benefit from undertaking hysterectomy in this situation and radical excision of the cervix would be overtreatment for this very early stage of cervical cancer as per NHS CSP guidelines. The majority of low volume, microscopic 1a1 tumours in the UK are diagnosed after LLETZ procedures following screening (screen-detected cancers). A LLETZ is sometimes	

			repeated to ensure that excision margins were clear of both invasive and pre-invasive disease (cervical intra-epithelial neoplasia). In this situation, a simple hysterectomy is also considered if there were additional benign indications for the procedure or if the patient desired this as treatment if her family was complete. In this scenario, as there is very low clinical suspicion of residual carcinoma, it would be entirely reasonable for a hysterectomy to be offered as minimally invasive procedure (total laparoscopic hysterectomy (TLH) or laparoscopically assisted vaginal hysterectomy (LAVH) or robotically assisted total hysterectomy). In the quoted LACC trial only 1.6% of the patients belonged to the stage Ia1 group and therefore it is difficult to extrapolate the trial findings for those patients with very early disease. 2) Women desiring fertility preservation The fertility sparing options available to women with early stage cervix cancer ranges from LLETZ to a radical trachelectomy depending upon the dimension and stage of tumour. By definition, this interventional procedure guidance does not apply to women who wish fertility sparing surgery. It would be helpful if this issue is clarified in NICE guidance. 3) Women with early stage cervical cancer managed by simple hysterectomy The revised 2018 FIGO staging classification for cervix cancer has changed in two significant respects for stage 1a and 1b cancers (previously FIGO 2009). There is no longer a restriction of horizontal spread to <7mm to limit stage 1a cervix cancers. Tumours of any horizontal spread confined to the cervix and of measured stromal invasion <3mm in depth are classified as stage 1a1 and tumours with measured stromal invasion □3 and <5mm in depth are classified as stage 1a2. Stage 1b cervix cancers are now classified as lesions limited to the cervix with a measured stromal invasion □5mm – cancers of	

			<2cm maximum dimension are stage 1b1, cancers of □2cm and <4cm maximum dimension are stage 1b2 and cancers with a maximum dimension □4cm are stage 1b3. The extent of radicality of the local resection in stage 1b1 (FIGO 2018) cervix cancers has been an issue of debate in the gynaecological oncology community. Two randomised controlled trials found that following a less radical approach in terms of a Piver-Rutledge type I instead of III (Piver 1 or 2 – Class A/B) has equal oncologic safety but a lower surgical morbidity profile. Wright et al found that patients with cervical cancer less than 2cm with no LVSI and negative pelvic nodes had only 0.4% risk for parametrial invasion and, therefore, could have received simple hysterectomy. Based on this and similar retrospective studies, three prospective randomised clinical trials have been designed to study the role of less radical surgery in this patient group. The largest recruiting trial currently is the SHAPE Trial (ClinicalTrials.gov Identifier: NCT01658930), a randomized Phase III Trial Comparing Radical Hysterectomy and Pelvic Node Dissection vs Simple Hysterectomy and Pelvic Node Dissection in Patients With Low-Risk Early Stage which is open to recruitment in the United Kingdom with 700 planned patients and an estimated recruitment completion date by 2020. Thus, the international community would accept a women being offered simple hysterectomy for early stage cervical cancer (FIGO 1A2/IB1, FIGO 2018) as potentially equivalent in cancer survival, subject to further trial evidence. We encourage recruitment to SHAPE in this group of patients. In summary, options for the management of early stage cervical cancer < 2 cm include (non-fertility sparing): 1. LLETZ for Stage 1A1 cervical cancer 2. Total laparoscopic hysterectomy for stage 1a2/ Stage 1B1 cervix cancer (FIGO 2018) after complete excision from previous diagnostic LLETZ procedure, usually in the context of a trial. 3. Laparoscopic radical hysterectomy for stage 1b1 cervix cancers, after complete excision from previous diagnostic	

			LLETZ procedure, following careful counselling and reference to the LACC study. 4. Open radical hysterectomy for 'at least' stage 1b1 (incomplete excision) FIGO 2018 cervix cancers. ***In our opinion, a blanket ban on minimal access surgery would be deleterious in the management of women with cervical cancer < 2 cm, potentially subjecting women to the morbidity of unnecessary open surgery, increasing hospital stay, increasing NHS resource use, without any benefit to cancer survival.*** **Evidence on minimal access radical hysterectomy - work to inform guidance** A more detailed analysis of the NCRAS cervix cancer data is currently being undertaken with access to the full cellular pathology reports to allow assessment of outcomes based on tumour dimensions using both diagnostic and treatment specimens. The BGCS awaits this data from England, which will provide us with best available evidence to guide management for women with cervical cancer < 2 cm. ***We urge NICE to support this effort and to defer final guidance on women with cervical cancer < 2 cm after this data is available.*** The European SUCCOR study has also demonstrated that patients with tumours smaller than 2 cm and those with previous cone biopsy did not show differences in disease free survival (DFS) by the surgical approach. Furthermore, the use of a uterine manipulator in MIS impacted the DFS negatively in this population. Interestingly, patients that underwent radical hysterectomy by MIS without the use of a manipulator showed the same outcome to those operated by open surgery. Protective manoeuvres to avoid tumour spillage at the time of the colpotomy in MIS improved the DFS in these patients. The findings of the SUCCOR study correlated with the intuitive hypotheses of the gynaecological oncological community, that the potential reasons of the	

			negative impact of MIS in the LACC study, are probably related to the surgical manipulation of the tumour during dissection and extraction and also applicable therefore in larger tumours. We acknowledge that case reporting by individual centres and retrospective audit methodology may influence SUCCOR results. **Conclusion** The BGCS acknowledges the concerns of the patient organisation (Jo's cervical Cancer Trust) about the existing BGCS position statement; that it is '*unreasonable to expect patients to be able to make such a difficult decision about their treatment. The guidance currently relies entirely on the ability of clinicians to fully communicate risks and benefits without any bias and without access to robust research and data outcomes. This will make an already incredibly difficult time for women far more stressful.*' Still, as per the Montgomery ruling, we as a medical community need to respect and take into consideration the right of patients to receive all knowledge about all potential therapeutic alternatives for their condition, so that they themselves can make an informed decision about what treatment is best suited for them. The BGCS is committed to fully informed decision making by patients; we undertake to work with NICE to draft appropriate Patient information so women and their families can make informed choices. We will work with NICE to agree a minimum dataset that must be collected by centres offering minimal access radical hysterectomy for cervical cancer < 2 cm to demonstrate safety both to patients and to hospital trusts. Finally, we are fully prepared to revise our position if NCRAS data demonstrates that survival is compromised in women undergoing minimal access surgery in cervical cancer < 2 cm. ***In summary, we would urge NICE to recognise the uncertainty of current evidence as applicable to women with tumours < 2 cm and the potential harms that would result from an outright cessation of minimal access***	

			surgery in this group. We fully support NICE position in cessation of minimal access surgery in women with tumours > 2 cm. References Robot-assisted Approach to Cervical Cancer (RACC) Study https://clinicaltrials.gov/ct2/show/study/NCT03719547?show_desc=Y#desc (accessed 12th November 2019 Falconer H, Palsdottir K, Stalberg K, Dahm-Kähler P, Ottander U, Lundin ES, Wijk L, Kimmig R, Jensen PT, Zahl Eriksson AG, Mäenpää J, Persson J, Salehi S. Robot-assisted approach to cervical cancer (RACC): an international multi-center, open-label randomized controlled trial. Int J Gynecol Cancer. 2019 Jul;29(6):1072-1076. doi: 10.1136/ijgc-2019-000558. Epub 2019 Jun 14. Comparisons of overall survival in women diagnosed with early stage cervical cancer during 2013-2016, treated by radical hysterectomy using minimal access or open approach. National cancer Registration and Analysis Service (Public Health England). https://www.bgcs.org.uk/wp-content/uploads/2019/07/NCRAS-cervical-cancer-surgery-analysis-May-2019-final.pdf (accessed 12th November 2019) BGCS Position Statement on Laparoscopic Radical Hysterectomy for Cervical Cancer (May 2019) https://www.bgcs.org.uk/wp-content/uploads/2019/07/NCRAS-mas-v-open-radical-hysterectomy-BGCS-professionals-statement-May-2019-1.pdf (accessed 12th November 2019) Landoni F, Maneo A, Zapardiel I, Zanagnolo V, Mangioni C. Class I versus class III radical hysterectomy in stage IB1-IIA cervical cancer. A prospective randomized study. Eur J Surg Oncol. 2012 Mar;38(3):203-9. Landoni F, Maneo A, Cormio G, Perego P, Milani R, Caruso O, Mangioni C. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. Gynecol Oncol. 2001 Jan;80(1):3-12.	

			Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895-904. DOI: 10.1056/NEJMoa1806395 Martin-Hirsch P, Wood N, Whitham NL, Macdonald R, Kirwan J, Anagnostopoulos A, Hutson R, Theophilou G, Otify M, Smith M, Myriokefalitaki E, Quinland W, Mahon-Daly F, Clayton RD, Nagar H, Harley I, Dobbs S, Ratnavelu N, Kucukmetin A, Fisher AD, Tailor A, Butler-Manuel S, Madhuri K, Edmondson R. Survival of women with early-stage cervical cancer in the UK treated with minimal access and open surgery. BJOG. 2019 Jul;126(8):956-959. doi: 10.1111/1471-0528.15617. Epub 2019 Mar 1. SHAPE: A randomised phase III trial comparing radical hysterectomy and pelvic node dissection vs simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer. http://www.ctc.ucl.ac.uk/TrialDetails.aspx?Trial=106& Chiva L et al, ESGO 2019 Plenary Presentation. https://ijgc.bmj.com/content/29/Suppl_4/A1 (accessed 19/11/2019) Public Health England, https://www.bsccp.org.uk/assets/file/uploads/resources/NHSCSP_20_Colposcopy_and_Programme_Management_(3rd_Edition)_(2).pdf (accessed 19/11/2019) Montgomery v Lanarkshire Health Board [2015] SC 11 [2015] 1 AC 1430. https://www.supremecourt.uk/cases/docs/uksc-2013-0136-judgment.pdf Accessed 19/11/2019	
3	Consultee 3 NHS Professional	**General**	I am writing on behalf of myself and my Christie Hospital consultant gynaecological oncology surgical colleagues [redacted], [redacted], [redacted] who have read and agree with the comments. We have several issues with the proposed guidance.	Thank you for your comments. Consultee disagrees with main recommendation.

			The guidance was based on numerous trials but heavily weighted by the outcome of the LACC trial and the recent pooled HES data from the UK. Although we acknowledge that the results of the LACC trial cannot be ignored, the LACC trial was flawed. There were numerous problems with the trial protocol and therefore interpretation of its results. 1. The LACC trial was in effect a laparoscopic trial not a robotic trial (More than 80% of patients in minimal access arm were laparoscopic.) 2. The LACC trial recruited participants from 33 centers worldwide during nine years. Although the protocol required accreditation of participating surgeons, internal validity can be questioned. This is supported by the fact that all recurrences in MIS arm were concentrated to 13 centres. In the UK, cervical cancer treatment is centralised to tertiary referral centres resulting in high-volume centres. 3. The LACC trial did not report on size of parametrium obtained at radical hysterectomy and therefore adequacy of surgery for each individual patient cannot be assessed objectively. 4. The LACC trial did not get a centralised pathology review. 5. The LACC trial allowed any type of uterine manipulators, including intra-uterine devices. Evidence has been presented at ESGO, after the NICE consultation has gone out, that it may be the use of uterine manipulators that causes an increase in disease recurrence rather than the fact that the procedure is performed by minimal access techniques. 6. With respect to the reivew of HES data, it will necessarily pool the national experience including those centres in which the enthusiastic adoption of lap radical hysterectomy was not necessarily matched by surgical quality assurance. This therefore may have an impact on the overall results obtained.	The main recommendation was changed.

			The BJOG paper (Martin Hirsch et al Survival of women with early-stage cervical cancer in the UK treated with minimal access and open surgery BJOG March 2019) that looked at the practice within the UK in high volume centres showed no difference in recurrence and survival between open and minimal access arms. A strong unequivocal statement that says minimal access surgery for cervical cancer is inferior to open surgery with respect to disease recurrence and survival would be incorrect on the information available at present and would effectively end recruitment into future trials. We believe that centres that have prospective data capture that can demonstrate favourable outcomes for patients with (FIGO 2009 Stage 1b1) FIGO 2018 Stage 1b2 cervical cancer having robotic radical hysterectomy should be allowed to continue to offer this intervention in the context of clinical trials.	

Consultation 2				
Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
1	Consultee 1 NHS Professional	**1.1**	Regarding the draft recommendations - section 1.1 "The evidence on efficacy for tumours smaller than 2 cm is inconclusive for disease-free and overall survival compared with open hysterectomy surgery. Therefore, for tumours smaller than 2 cm this procedure should only be used in the context of research." It wold be important to distinguish that this is for radical hysterectomy, since the role of laparoscopic simple hysterectomy for Ia1 disease was not Ix in these studies. Otherwise this is a very sensible and clear document, based on the available data so far.	Thank you for your comment. 'Radical hysterectomy' is included in the title of the guidance. A committee comment has been added to clarify that the guidance does not cover laparoscopic simple hysterectomy for 1a1 disease.

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2	Consultee 2 Private sector professional	**General**	There is important literature missing, which can be cited with the key word "coelio-schauta", which is an alternative name for "Laparoscopic Radical Hysterectomy" For example our article Papacharalabous, E., Tailor, A., Madhuri, T. Giannopoulos, T., Butler-Manuel, S. Early experience of laparoscopically assisted radical vaginal hysterectomy (Coelio-Schauta) versus abdominal radical hysterectomy for early stage cervical cancer. Gynecol Surg 6, 113–117 (2009). https://doi.org/10.1007/s10397-008-0424-8	Thank you for your comment. Evidence on laparoscopically assisted radical vaginal hysterectomy was excluded from the overview, because it was considered to be a different procedure. Section 2.6 of the draft guidance states that 'The technique is distinct from laparoscopically assisted vaginal hysterectomy, which may include laparoscopic division of the infundibulopelvic ligaments and the uterine vessels before a vaginal hysterectomy is done.'

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3	Consultee 3 NHS Professional	**General**	British Gynaecological Cancer Society Response to the NICE Interventional Procedures Advisory Committee with respect to the consultation documentation considering Minimally invasive radical hysterectomy for early stage cervical cancer. [In development [GID-IPG10131] Expected publication date: 16 December 2020]. We thank NICE for being responsive to our previous comments on this important topic, and for giving us opportunity to act as stakeholders in this consultation and submit our response below. The British Gynaecological Cancer Society (BGCS) is the professional home of health providers working and researching the area of gynaecological cancers. Our members consist of medical practitioners, clinical nurse specialists and other allied professionals, including scientists who have an interest in gynaecological cancers. We represent trainees, nurses, unit leads, oncologists, pathologists and radiologists and have a total membership in excess of 400. The BGCS produces evidence-based guidelines for the management of gynaecological cancers that are peer reviewed through a panel of international referees. BGCS Council members are also representatives of the European Society of Gynaecological Oncology and the International Gynaecological Cancer Society. As a society, we are committed to supporting our members deliver the highest standards of care for women with cervical cancer.	Thank you for your comment.

Consultation 2				
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4	Consultee 3 NHS Professional	**General**	We have the following points to make: We are in agreement with this document, and believe that the recent evidence has been presented in a very clear and sensible manner.	Thank you for your comment.
5	Consultee 3 NHS Professional	**1.1**	Regarding the draft recommendations – Section 1.1 "The evidence on efficacy for tumours smaller than 2 cm is inconclusive for disease-free and overall survival compared with open hysterectomy surgery. Therefore, for tumours smaller than 2 cm this procedure should only be used in the context of research." It wold be important to distinguish that this is for radical hysterectomy, since the role of laparoscopic simple hysterectomy for Stage 1a1 disease was not investigated in these studies.	Thank you for your comment. 'Radical hysterectomy' is included in the title of the guidance. A committee comment has been added to clarify that the guidance does not cover laparoscopic simple hysterectomy for 1a1 disease.
6	Consultee 3 NHS Professional	**2.5**	Section 2.5 ''A uterine manipulator is inserted through the vagina and attached to the uterus and cervix.'' This should be modified to read 'a uterine manipulator is often inserted through the vagina…' as not all surgeons routinely use uterine manipulators that traverse the cervix, and the committee have rightly commented in section 3.6 '' that research into variations in the technique designed to reduce the risk of tumour seeding or other potential causes of long-term tumour recurrence may be appropriate.''	Thank you for your comment. Section 2.5 of the draft guidance has been changed.
7	Consultee 3 NHS Professional	**General**	We hope NICE will revisit this guidance if data changes on this subject, especially in the group with tumour volume < 2 cm.	Thank you for your comment. Procedures with 'research only' recommendation may be reassessed when relevant new research is published.

8	Consultee 4 Company	**1.1**	Response to NICE GID-IPG10176: We would like to thank the NICE IPAC for the time devoted to this very important subject. We understand the limited time and resources in these challenging times and welcome the rapid review. Our literature review (attached) is intended to supplement this submission with additional data and a detailed meta-analysis. **<u>Response to recommendation 1.1:</u>** **Overall survival** We have performed a systematic literature review and meta-analysis on publications reviewing long term outcomes [cancer recurrence, disease free survival (DFS) and overall survival (OS)) for women that underwent robot assisted (RRH), laparoscopic (LRH) or open (ORH) surgery for radical hysterectomy for cervical cancer]. The review looked at studies published from January 1, 2010 to November 18, 2019 in Embase, PubMed and Scopus databases. We included studies that are Randomised Control Trials (RCTs), Meta-Analysis/Systematic Reviews, independent database reviews and comparative studies reporting on robotic-assisted, minimally invasive, laparoscopic and/or open surgery. We excluded studies that: were not in English, analyzed data that was not stratified by study arms, looked at alternative techniques/approach, analyzed hysterectomy data mixed with other non-hysterectomy data, did not provide quantitative results for the long term (>1year) recurrence and survival included redundant patient population and similar conclusions	Thank you for your comment. The procedure description states that a robot may be used to assist with the procedure. The Committee considered this comment but decided not to change the guidance.

			Of the thirty-four (34) full text publications identified, twenty-nine (29) publications reported original research results and five (5) publications reported the results from separate meta-analyses (please see the bibliography at the end of this response). The twenty-nine (29) original research publications were evaluated in pooled meta-analyses. Meta-analyses and graphical representation of the data abstracted from the original research publications were prepared using Review Manager (RevMan) software version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). Hazard ratios (HRs) and Relative Risks (RR) are presented with 95 percent confidence intervals. Hazard Ratios (HRs) were either directly obtained from the original research publications or estimated based on the available data from time-to-event analyses. Robotic Radical Hysterectomy (RRH) vs Open Radical Hysterectomy (ORH): Fifteen (15) articles reported on recurrence comparing robotic and open cohorts. The follow-up period ranged from 12 to 120.9 months. Thirteen (13) articles reported on DFS and thirteen (13) reported on OS between the robotic and open cohorts. **The meta-analysis showed no statistically significant differences in DFS or OS between the two cohorts. Additionally, the meta-analysis showed that the robotic cohort had a statistically significant benefit for recurrence in comparison to the open cohort.** Recurrence [Number of patients: RRH=1,876, ORH=1,563] Risk Ratio (RR) is 0.79 (95% CI 0.65 to 0.97), p=0.02. RRH significantly improves recurrence; 3% is the minimum improvement consistent with these data. Only 2/15 publications reported a time to event analysis on recurrence, so RR was used to include the 15 publications with information on this endpoint.	

			Disease-free survival [Number of patients: RRH=1,654, ORH=1,583] Hazard Ratio (HR) is 0.95 (95% CI 0.69 to 1.30), p=0.76. No statistically significant difference observed. The risk of cancer recurrence or death for robotic compared to open lies between 31% better and 30% worse. Overall survival [Number of patients: RRH=2,653, ORH=2,554] Hazard Ratio (HR) is 1.13 (95% CI 0.90 to 1.42), p=0.28. No statistically significant difference observed. The risk of death for RRH compared to ORH lies between 10% better and 42% worse. Robotic Radical Hysterectomy (RRH) vs Laparoscopic Radical Hysterectomy (LRH): Sixteen (16) articles reported on recurrence comparing robotic and minimally invasive/laparoscopic cohorts. The follow-up period ranged from approximately 12 to 69 months. Ten (10) articles reported on DFS and nine (9) articles reported on OS between the robotic and minimally invasive/laparoscopic cohorts. **The meta-analyses showed no statistically significant differences in recurrence, DFS and OS between the two (2) cohorts**. Recurrence [Number of patients: RRH=911, LRH=2,011] Risk Ratio (RR) is 0.0.97 (95% CI 0.75 to 1.25), p=0.83. No statistically significant difference observed. However, no time to event analyses were performed in the sixteen (16) publications that reported on recurrences. Disease-free survival [Number of patients: RRH=608, LRH=939] Hazard Ratio (HR) is 1.21 (95% CI 0.90 to 1.62), p=0.21. No statistically significant difference observed. The risk of cancer recurrence or death for RRH compared to LRH lies between 10% better and 62% worse.	

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			Overall survival [Number of patients: RRH=662, LRH=874] Hazard Ratio (HR) is 1.13 (95% CI 0.72 to 1.77), p=0.61. No statistically significant difference observed. The risk of death for RRH compared to LRH lies between 28% better or 77% worse. A sensitivity analysis demonstrated that these results were consistent using either unadjusted or adjusted Hazard Ratios. For transparency, we have provided this committee with the detailed methods of the above-mentioned meta-analysis, along with additional results (in the attached tables and forest plots).	

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9	Consultee 4 Company	**General**	**Tumour size 2 cm cut-off** From 34 studies we have reviewed as part of our systematic literature review, only Melamed et al. 2018 conducted a subset analysis for survival tumour size of =2cm. We feel that there is not enough evidence to conclude on a cut-off of 2cm. In fact, there are recent studies that concluded that survival rates are similar regardless of the tumour size (Wenzel et al. 2020, **https://www.sciencedirect.com/science/article/pii/S0959804920301957**). We feel that there is insufficient evidence and strongly believe that additional research is necessary to make recommendations on tumour size cut off of 2 cm.	Thank you for your comment. Consultee disagrees with having separate recommendations according to tumour size. The Committee considered this comment but decided not to change the guidance. A tumour size cut-off of 2 cm was used in 4 studies in table 2 of the overview (Melamed, 2018; Kim SI, 2019; Kim SI, 2019b, Martin-Hirsch P, 2019). Several recently published studies have presented survival analysis by tumour size, using a cut-off of 2 cm (Chen C, 2020; Li P, 2020 and Chiva L, 2020). 2 cm was also suggested as a cut-off by consultees during the first consultation on draft guidance for this procedure, when the draft recommendation was that the procedure should not be used. Wenzel et al., 2020 was identified in the updated literature search and will be added to the appendix of the overview.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."