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The recent publication of two papers and an editorial in the New England Journal of Medicine (NEJM) (1-3) has caused consternation in the gynaecological oncology community (4, 5). Both papers demonstrate a worse outcome for patients undergoing radical hysterectomy by the minimal access route compared to open surgery and thus question the dominant paradigm of the last decade that minimal access surgery is the preferred method by which to carry out radical surgery for cervical cancer. These studies raise many questions but the two most pressing are, firstly, have our patients been disadvantaged by our adoption of minimal access surgery and, secondly, how do we proceed as a gynaecological oncology community in the face of these data?

Route of surgery for radical cervical surgery has been controversial for some time. Attempts to introduce a laparoscopically assisted radical vaginal hysterectomy in the 1990s were abandoned as it was generally felt to be less radical than the open procedure (6). Further developments in laparoscopic technique however allowed the development of the total laparoscopic radical hysterectomy which was introduced in the early part of this century (7). This operation has been adopted by many centres and has rapidly become the operation of choice for most surgeons and patients.

However, in common with many other surgical procedures, this operation has been introduced on the basis of non randomized data, the evidence to support its use largely being in the form of retrospective data collections, reviewed in (8, 9). These have been universally favourable until now when these two, independent, studies demonstrate a poorer outcome for patients who have undergone radical surgery via a minimal access route (1, 2). The first of these is the study by Ramirez et al (1), the Laparoscopic Approach to Cervical Cancer (LACC) study, a large, well designed international phase III trial. This trial was stopped early after an interim analysis showed a lower disease free interval in the minimal access (MAS) arm. Final analysis has confirmed this and shown a worse overall 3 year survival (93.8% vs 99.0%, hazard ratio, 6.00) for patients treated with minimal access surgery. These findings are supported by the epidemiological data presented by Melamed and colleagues (2) in the second of the NEJM papers.

During the time this trial recruited minimal access surgery has been widely introduced in the UK and elsewhere and patients, and clinicians, will naturally question whether care has been compromised by this move. We therefore felt it important to carry out a pragmatic analysis to ensure that UK practice wasn't harming patients. To achieve this we undertook a comprehensive analysis of the outcomes for patients being treated for stage 1B1 cancers in eight major tertiary referral centres in the UK.

To demonstrate that patients care had not been compromised we compared the outcomes for patients undergoing surgery in these eight centres, by whatever route, to the superior arm (open surgery) of the LACC study.

The UK cohort

A total of 779 cases of stage 1B1 cervix cancer were collated for our analysis. The clinical characteristics of the cases submitted are shown in table 1. In comparison to the cases in the control arm of the LACC study (1) there were significant differences in the proportion of women with squamous tumours (56% (UK) vs 67% (LACC), $p<0.01$), low grade tumours (22% vs 10%, $p<0.05$), presence of LVSI (37% vs 29%, $p<0.05$) and tumours less than 2cm in diameter (58% vs 52%, $p<0.01$).

597/779 (77%) of cases were treated with radical hysterectomy and of these 463/779 (78%) were treated with a laparoscopic or robotic approach, . Of the remainder, 7% were treated with simple hysterectomy, 6% with radical trachelectomy and 8% with a conisation procedure. All patients underwent a lymph node assessment, usually in the form of a systematic pelvic node dissection, as part of their surgical management.

Survival in the UK cohort

With a median follow up time of 23 months there were 36/779 (4.6%) recurrences and 11/779 (1.4%) deaths (all cause) in the cohort, figure 1. The majority of the recurrences occurred early in the follow up period, in line with the control arm of the LACC study, and in contrast to the minimal access arm of the LACC trial which has shown a linear cumulative recurrence (1).

There were no differences in mortality rates between those patients treated with an open (3/130,2.3%), laparoscopic (6/366, 1.6%), or robotic (2/97,2.1%) approach. Although mortality was not associated with route of surgery there was an association between size of tumour, and the presence of LVSI, table 2. However there was no association between grade or histotype of tumour and mortality, table 2.

Comparison with LACC

The hypothesis that overall survival in UK patients is equivalent to that seen in the control arm of the LACC study is supported by the crude survival statistics of 11/779 (1.4%) in our UK series compared to 3/312 (0.96%) in the LACC study.

However, to account for the differences in the clinical characteristics between the UK series and the LACC control arm, outlined in table 1, a logistic regression model was created using 573 cases from the UK series for which there were complete data for histotype, grade of tumour, patient age, presence of LVSI and size of tumour. The model was then run using the clinical characteristics taken from the LACC study which are shown in table 1. This resulted in a relative risk increase of 1.27 in death rate which, when applied to the UK series data, increases the mortality rate from 1.40% to 1.78%, still substantially less than the 5.2% seen in the MAS arm of LACC. Thus, this gives confidence that even correcting for clinical characteristics the survival rate remains high, and in line with the control arm of the LACC study.

We can thus be confident that in eight major teaching hospitals in the UK overall survival is high (98.6%) and is comparable to that seen in the control arm of the LACC trial, despite over 75% of the patients being treated with a minimal access approach. The follow up times were very similar between the two cohorts. The recurrence rate in our series is somewhat higher than that seen in the LACC study and the implication of this will require prolonged follow up.

Given that we have shown no difference between open and minimal access surgery in our series this gives confidence in our current pattern of care, but there now remains the question of how the LACC results should be interpreted and how these results should inform future clinical practice.

Applying the results of randomized controlled trials is not always entirely straightforward and there may be good reasons why the external validity of a trial is low thus preventing application of the results to the whole patient population (10). These can be summarized as the setting of the trial, the selection of patients, the characteristics of randomized patients, differences between the trial protocol and routine practice, outcome measures and follow up, and adverse effects of treatment (10)

It is interesting to note that in the study by Melamed and colleagues (2) size of tumour was the strongest prognostic factor, with tumours greater than 2cm carrying a worse prognosis when operated upon laparoscopically and although this is supported in our UK data this is not borne out in the LACC study with similar death rates seen for tumours of all sizes. Nevertheless it may be that treatment should differ for tumours less than 2cm in size which may remain amenable to a minimal access approach, this is facilitated by the new FIGO staging (11). Indeed management of these tumours may be subject to change following the completion of the international SHAPE trial investigating the role of simple hysterectomy in this cohort of tumours.

We are left therefore considering whether the difference in our results is related to a difference in our minimal access approach. There is little standardization of the technique of radical laparoscopic hysterectomy and it is possible that, given that no UK centres participated in the LACC study, that UK practice is somewhat different from than that carried out within the trial. The LACC study had a learning curve built into the study design including video assessments of the procedures. This was a commendable feature of the randomized study but it still remains challenging to control for variances in surgical practice. Recent advances in this field describe the development of detailed typologies to standardize delivery of surgical interventions in trials (12) and the development of such a typology may be pertinent for any future studies of radical hysterectomy . Moreover, there was no report in the LACC study of the radicality of each procedure. Future studies should include measurements of parametrium and ligament length to examine whether the differences seen are related to a feature of minimal access surgery such as the use of a uterine manipulator or whether minimal access surgery is just fundamentally less radical.

Even if we can be satisfied that patients have not come to significant harm through our use of minimal access surgery we need to now consider how to use the available evidence to formulate guidelines for the future. The possible explanations for the findings in the LACC study outlined above remain conjectures and until further evidence becomes available we are in a position that the only grade A evidence favours open surgery. In the forthcoming debates it will be easy to state that patients should be shown the evidence and allowed to decide, but this is to hide behind the mantra of patient choice. Patients look to us for advice and we need to be clear as to what that advice will be. Are we going to advocate a complete return to open surgery, selection criteria for those who can safely be treated with MAS, or further clinical trials to add to the evidence base? Accruing funding for a further clinical trial would be challenging but equally a complete abandoning of minimal access surgery would seem to be a step too far. It is our opinion that patient selection criteria can be developed, based on the presence or absence of risk factors, that would allow safe selection of those patients who can safely be treated with minimal access surgery.

In the interim we suggest that each health economy/jurisdiction currently practicing minimal access radical hysterectomy should carry out a similar benchmarking exercise to our current study to ensure that their practice is achieving optimal outcomes. Our data provide important information that, in the UK at least, survival rates have remained high following the introduction of minimal access surgery and continue to be at the highest levels seen in any series. Individual clinicians will now need to weigh all of this evidence carefully to allow them to be able to guide their future patients.

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Disclosure of interests

MS, AT and SB-M are all preceptors for Intuitive Robotic Surgery

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Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

RJE, PMH, NW, RM, MS and RH conceived and designed the UK observational study

PMH, NW, NLW, RM, JK, AA, RH, GT, MO, MS, EM , WQ, FM-D ,RDC, HN, IH, SD, NR, AK, ADF, AT, SB-M, KM & RJE contributed to data collection and verification.

RJE and PMH undertook the analysis

PMH, NW, NLW, RM, JK, AA, RH, GT, MO, MS, EM , WQ, FM-D ,RDC, HN, IH, SD, NR, AK, ADF, AT, SB-M, KM & RJE reviewed and contributed to the manuscript

Details of ethics approval

Ethical approval was not sought as this was a retrospective observational study of practice

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Table 1 – clinical characteristics of UK cohort and comparison against control arm of LACC

		UK series		LACC study[a]		P
		n	%	n	%	
Age						
	Median	**40**		**46**		
	Range	**23-88**				
Histological type						
	Squamous	**416**	**56**	**210**	**67**	**<0.01**
	Adeno	**252**	**35**	**80**	**27**	
	Mixed	**28**	**4**	**6**	**2**	
	Other	**27**	**4**			
	Not recorded	**56**		**16**		
Grade						
	1	**129**	**22**	**29**	**10**	**<0.05**
	2	**278**	**47**	**111**	**39**	
	3	**185**	**31**	**61**	**22**	
	Not recorded	**187**		**81**	**29**	
LVSI						
	Present	**289**	**37**	**81**	**29**	**<0.01**
	Absent	**406**	**52**	**185**	**66**	
	Not recorded	**84**	**11**	**16**	**6**	
Size of tumour						
	<2cm	**452**	**58**	**147**	**52**	**<0.01**
	>=2cm	**256**	**33**	**121**	**43**	
	Not recorded	**71**	**9**	**14**	**5**	

a- data from control arm (open surgery) within LACC study, taken from (1)

Table 2 – prognostic factors in the UK cohort

		Number	Deaths	Rate (%)	P
Histotype					
	Squamous	338	3	0.89	NS
	Adeno	200	5	2.5	
	Mixed	34	2	5.9	
Grade					
	1	134	2	1.5	NS
	2	262	2	0.76	
	3	175	6	3.4	
LVSI					
	Present	296	7	2.4	<0.01
	Absent	407	1	0.2	
Size					
	<2cm	452	3	0.6	<0.01
	>=2cm	256	8	3.1	

Figure 1

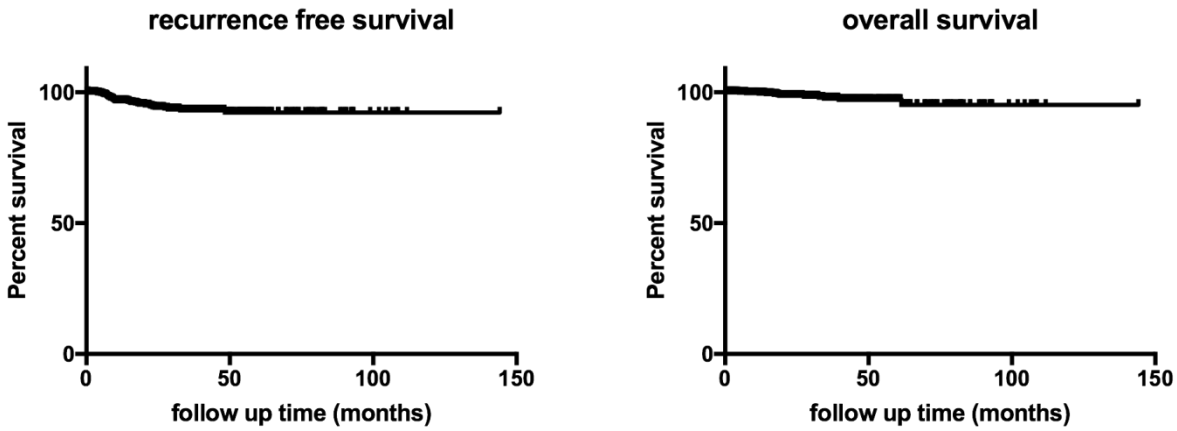

Figure 1: Kapan Meier curves showing recurrence free survival and overall survival for 779 patients with stage 1B1 cervix cancer with a median follow up of 23 months.