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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

Executive summary

Purpose and context

Given published evidence suggesting possible survival differences by type of surgical approach in early stage cervical cancer,[1,2] NCRAS was asked to examine English population-based data on women treated by either minimal access or open surgery.

Methods

Cohort definition: Women resident in England with early stage diagnosis (IA2, IB, IB1) of cervical cancer treated surgically by either minimal access or open approach and diagnosed during 2013-2016 formed the analysis cohort. The diagnosis era (2013-2016) represents the first period in which analysis could be performed using highly complete nationwide information on stage at diagnosis.

Outcomes: Overall survival information, and time to death where applicable, are based on NCRAS data with ONS mortality file linkage. All patients were followed up to end of 2017 (follow-up range 129-1824 days, median 1116 days, mean 1109 days).

Exposure variables:

Definition of treatment groups: This was principally based on linked cancer registration and Hospital Episodes Statistics (HES) data, using OPCS-IV procedure classification codes to define whether the surgical approach was by minimal access or open. Additionally, Systemic Anti-Cancer Therapy (SACT) and Radiotherapy Dataset (RTDS) data was used to define whether surgically treated patients also received adjuvant therapy with either or both modalities (i.e. chemotherapy, radiotherapy) during the first 9 months from diagnosis.

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[1] Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, Buda A, Yan X, Shuzhong Y, Chetty N, Isla D, Tamura M, Zhu T, Robledo KP, Gebski V, Asher R, Behan V, Nicklin JL, Coleman RL, Obermair A. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. N Engl J Med. 2018;379(20):1895-1904. doi: 10.1056/NEJMoa1806395. https://www.ncbi.nlm.nih.gov/pubmed/30380365

[2] Melamed A, Margul DJ, Chen L, Keating NL, Del Carmen MG, Yang J, Seagle BL, Alexander A, Barber EL, Rice LW, Wright JD, Kocherginsky M, Shahabi S, Rauh-Hain JA. Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer. N Engl J Med. 2018;379(20):1905-1914. doi: 10.1056/NEJMoa1804923. https://www.ncbi.nlm.nih.gov/pubmed/30379613

Information was also available on patient or tumour characteristic variables (including age at diagnosis, deprivation group, Charlson comorbidity group, stage at diagnosis, and Route to Diagnosis).

Analysis:
The patient and tumour characteristics, and adjuvant treatment status, of patients treated by either surgical approach were described. Logistic regression was used to examine the odds of treatment by minimal access (vs. open) surgery, by these characteristics.

Kaplan-Meier univariate analyses was performed by treatment group, and was additionally stratified by adjuvant treatment status and early stage category. Lastly, univariate and multivariate Cox regression analysis for mortality during follow-up was performed.

Findings

After excluding 10 patients (5 in either surgical approach group) with evidence of neo-adjuvant treatment, the analysis cohort comprised 929 women, representing 8.9% of all incident cases (cervical cancer) in the study era (n=10,409, 2013-2016). Among all incident (10,409) cases, stage completeness was 88.0%, noting that it was 100% among patients treated with minimal access surgery.

In the study cohort of 929 women, 564 (61%) were treated by the minimal access approach, and 365 (39%) by open surgery. The use of minimal access surgery increased from 48% in 2013 to 74% in 2016 (with reciprocal decrease in use of open surgery in our cohort). Considering the examined patient and tumour characteristics, there was generally little difference between the minimal access and the open surgery groups, with a small, though not statistically significant differences in use of adjuvant therapy, this percentage being 14.4% in the minimal access and 18.1% in the open surgery group.

Kaplan-Meier analysis indicated evidence for an association between surgical approach and survival during follow-up, with patients treated by the minimal access group having worse outcomes. Specifically, overall survival at 3 and 6 months, and 1, 2, 3, 4 and 4.5 years were as following:

	3 months	**6 months**	**1 year**	**2 years**	**3 years**	**4 years**	**4½ years**
Minimal access surgery (MAS) group	100.0%	99.8% (98.8-100.0)	99.1% (97.9-99.6)	96.6% (94.6-97.9)	94.7% (92.0-96.5)	93.9% (90.6-96.1)	93.1% (89.2-95.6)
Open group	100.0%	100.0%	99.7% (98.1-100.0)	99.4% (97.7-99.9)	98.3% (95.9-99.3)	98.3 % (95.9-99.3)	97.2% (93.0-98.9)
p-value	n/a	n/a	0.583	0.081	0.111	0.028	0.007

Differences by surgical approach where similar when stratifying the analysis by early stage category. When stratifying the analysis by adjuvant treatment status, differences between the two surgical approach groups were more pronounced among women treated with adjuvant management.

Unadjusted Cox regression analysis indicated evidence for variation in outcomes by surgical approach, with the minimal access group having a hazard ratio value of 3.3 (p=0.009). In multivariate Cox regression analysis adjusting for diagnosis year, age, socio-economic status, Charlson comorbidity score, stage at diagnosis, English region, Route to Diagnosis, and adjuvant treatment status the difference in outcomes between the two surgical approach groups remained, becoming slightly larger (hazard ratio value of 4.0, p=0.007).

Conclusion and interpretation

The findings broadly concord with prior peer-reviewed literature, indicating that in the context of overall excellent prognosis among women with early stage cervical cancer (4.5-year overall survival being 93% or greater) surgical approach is associated with overall survival, with women treated with the minimal access approach having inferior survival than those treated with open surgery.

Certain limitations of this analysis need to be acknowledged (and inform further analyses):
Assignment of treatment to either surgical access group is based on routine data (HES) and relies on accuracy of coding. Nonetheless, if potential misclassification of approach is random, this would be biasing comparisons towards the null, i.e. reducing as opposed to increasing observed differences.

Confounding by indication is a general concern in any type of observational data analysis, and the present analysis is not immune from such concerns. Nonetheless a range of case-mix variables of prognostic importance were adjusted for in analyses (including adjuvant treatment use, early stage category, diagnostic route, Charlson comorbidity group and age). While such adjustments do not preclude potential confounding by other variables, they can be deemed to minimise such concerns. Operator competence / skill and markers of surgical excision completeness do not form part of the present analysis. There was no adjustment for surgical experience and possible impact of learning curve for surgeons adopting minimal access surgery; laparoscopic and robotic surgery approaches within the minimal access group; and other surgical outcomes including surgical complication rates, and short- and long-term surgical morbidity.

Among exposure (case-mix) variables, adjuvant therapy status (which both generally, i.e. in external evidence, and within the studied cohort, was associated with greater risk of mortality), is reliant on information derived from the SACT and RTDS datasets, and their levels of accuracy and completeness. Nonetheless, as for potential random misclassification of surgery type in HES data, potential random misclassification of adjuvant therapy status would be biasing comparison estimates towards the null.

The findings relate to overall (crude) survival (as opposed to net survival analysis adjusting for competing causes of mortality, other than cervical cancer). However, in the context of a cohort of women of relatively young age, and in the presence of adjustment for deprivation and Charlson morbidity group, the degree of possible differential bias resulting from competing mortality can be deemed small, although it cannot be precisely quantified with the present analysis.

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National Cancer Registration and Analysis Service

TECHNICAL APPENDIX

1. Cohort and variable definitions

All cases of invasive cervical cancer defined as ICD10 code C53 diagnosed between 2013 to 2016 in England, were extracted from Public Health England's Cancer Outcomes and Services Dataset (COSD).

Treatment

Treatment was identified using the National Cancer Registration and Analysis Service's standard operating procedure - CAS-SOP 4.4 linking treatment tables – chemotherapy, tumour resections and radiotherapy. This allows treatment flags to be created that record whether there was chemotherapy, tumour resection, or radiotherapy following a cancer diagnosis.

As well as using COSD, treatment data was supplemented using radiotherapy dataset (RTDS), the Systemic Anti-Cancer Therapy (SACT) dataset for chemotherapy and Admitted Patient Care Hospital Episode Statistics inpatient (HES) for surgical procedures. In combination with the COSD extract, this data was used to identify the first occurrence of any surgery, chemotherapy or radiotherapy combination. Dates were compared to identify the sequencing of treatment.

<u>Surgical treatment and approach definitions</u>

The following OPCS Classification of Interventions and Procedures version 4.2 codes recorded in any of the operation fields were used in operational definitions.

Radical hysterectomy: Q071 Abdominal hysterocolpectomy and excision of peri uterine tissue; Q072 Abdominal hysterectomy and excision of peri uterine tissue NEC

MAS (Minimal access surgery): Y508 Other specified approach through abdominal cavity; Y751 Laparoscopically assisted approach to abdominal cavity; Y752 Laparoscopic approach to abdominal cavity NEC; Y755 Laparoscopic ultrasonic approach to abdominal cavity; Y758 Other specified minimal access to abdominal cavity; Y759 Unspecified minimal access to abdominal cavity; Y753 Robotic minimal access approach to abdominal cavity

MAS conversion to open surgery: Y714 Failed minimal access approach converted to open.

The hysterectomy data and the MAS data were matched by date, so that radical hysterectomies were defined as MAS where the procedure dates matched; surgery flags were then further defined as open radical hysterectomy, MAS radical hysterectomy, or other surgery. Any MAS radical hysterectomies that were converted to open were classed as open radical hysterectomy. To be flagged in this way, a patient must have both a radical hysterectomy and failed MAS code (as detailed above).

Stage data

Stage at diagnosis information, using the FIGO classification system, was taken from the COSD tables. FIGO stage IB is recorded where the detailed size of the tumour was unavailable when registering the case.

Geographical data

A measure of socio-economic status for patients included in the analysis was assigned using their postcode of residence at the time of the diagnosis. The income domain of the Index of Multiple Deprivation (2015) was used to assign the deprivation score associated with the Lower Super Output Area (2011) of that postcode into population-weighted quintiles. The region of residence was also assigned based on postcode of residence.

2. Composition of the two groups by case-mix variable

2a. Sample composition

	MAS group	**Open group**
All patients	564	365
Age Group		
<30	76 (13.5%)	44 (12.1%)
30-39	183 (32.5%)	118 (32.3%)
40-49	180 (31.9%)	103 (28.2%)
50-59	76 (13.5%)	70 (19.2%)
60+	49 (8.7%)	30 (8.2%)
p-value (χ^2)	0.200	
Age continuous (years) - mean	41.9	42.6
p-value (t-test)	0.830	
Deprivation		
Least Deprived - 1	75 (13.3%)	51 (14.0%)
2	96 (17.0%)	64 (17.5%)
3	112 (19.9%)	77 (21.1%)
4	125 (22.2%)	81 (22.2%)
Most Deprived - 5	156 (27.7%)	92 (25.2%)
p-value (χ^2)	0.942	
Early stage category		
IB1	479 (84.9%)	297 (81.4%)
IB	71 (12.6%)	57 (15.6%)
1A2	14 (2.5%)	11 (3.0%)
p-value (χ^2)	0.360	
Adjuvant therapy stats		
Yes	81 (14.4%)	66 (18.1%)
No	483 (85.6%)	299 (81.9%)
p-value (χ^2)	0.129	
Morbidity		
Charlson score 0	523 (92.7%)	337 (92.3%)
1	24 (4.3%)	22 (6.0%)
2+	16 (2.8%	6 (1.6%)
Missing	1 (0.2%)	0 (0.0%)
p-value (χ^2)	0.336	
Year of diagnosis		
2013	125 (22.2%)	137 (37.5%)

	MAS group	Open group
2014	132 (23.4%)	104 (28.5%)
2015	159 (28.2%)	71 (19.5%)
2016	148 (26.2%)	53 (14.5%)
p-value (χ^2)	< 0.001	
Region		
North West	79 (14.0%)	75 (20.6%)
North East	49 (8.7%)	2 (0.6%)
Yorkshire and The Humber	44 (7.8%)	99 (27.1%)
East Midlands	61 (10.8%)	19 (5.2%)
West Midlands	96 (17.0%)	16 (4.4%)
East of England	28 (5.0%)	47 (12.9%)
London	53 (9.4%)	16 (4.4%)
South East	96 (17.0%)	59 (16.2%)
South West	58 (10.3%)	32 (8.8%)
p-value (χ^2)	< 0.001	
Diagnostic route		
Screening	275 (48.8%)	189 (51.8%)
EP	7 (1.2%)	2 (0.6%)
Planned referrals (TWW, GP referral, inpatient elective, other outpatient)	273 (48.4%)	170 (46.6%)
Unknown	9 (1.6%)	4 (1.1%)
p-value (χ^2)	0.561	

2b. Odds of receiving laparoscopy surgery compared to open surgery†

Complete Data:

	Odds Ratio (95% CI)	**p-value***
Diagnosis Year		
2013	REF	REF
2014	1.4 (0.9 – 2.1)	0.111
2015	2.9 (1.9 – 4.5)	< 0.001
2016	3.8 (2.4 – 6.0)	< 0.001
p-heterogeneity	< 0.001	
Age Group		
<30	REF	REF
30-39	0.9 (0.5 – 1.4)	0.569
40-49	0.9 (0.5 – 1.5)	0.726
50-59	0.5 (0.3 – 1.0)	0.035
60+	0.7 (0.4 – 1.5)	0.404
p-heterogeneity	0.171	
Deprivation		
Least Deprived - 1	REF	REF
2	1.0 (0.6 – 1.8)	0.868
3	0.9 (0.5 – 1.5)	0.743
4	0.8 (0.5 – 1.4)	0.534
Most Deprived - 5	1.1 (0.6 – 1.8)	0.767
p-heterogeneity	0.840	
Charlson Score		
0	REF	REF
1	0.8 (0.4 – 1.7)	0.630
2+	2.3 (0.8 – 6.6)	0.113
p-heterogeneity	0.222	
Stage		
IB1	REF	REF
IB	0.6 (0.4 – 1.0)	0.039
1A2	0.8 (0.3 – 1.9)	0.593
p-heterogeneity	0.112	
Region		
North West	REF	REF
North East	27.0 (6.2 – 117.2)	< 0.001
Yorkshire and The Humber	0.4 (0.2 – 0.6)	< 0.001
East Midlands	3.7 (1.9 – 7.1)	< 0.001
West Midlands	6.5 (3.4 – 12.5)	< 0.001
East of England	0.6 (0.3 – 1.1)	0.097
London	3.3 (1.7 – 6.5)	0.001

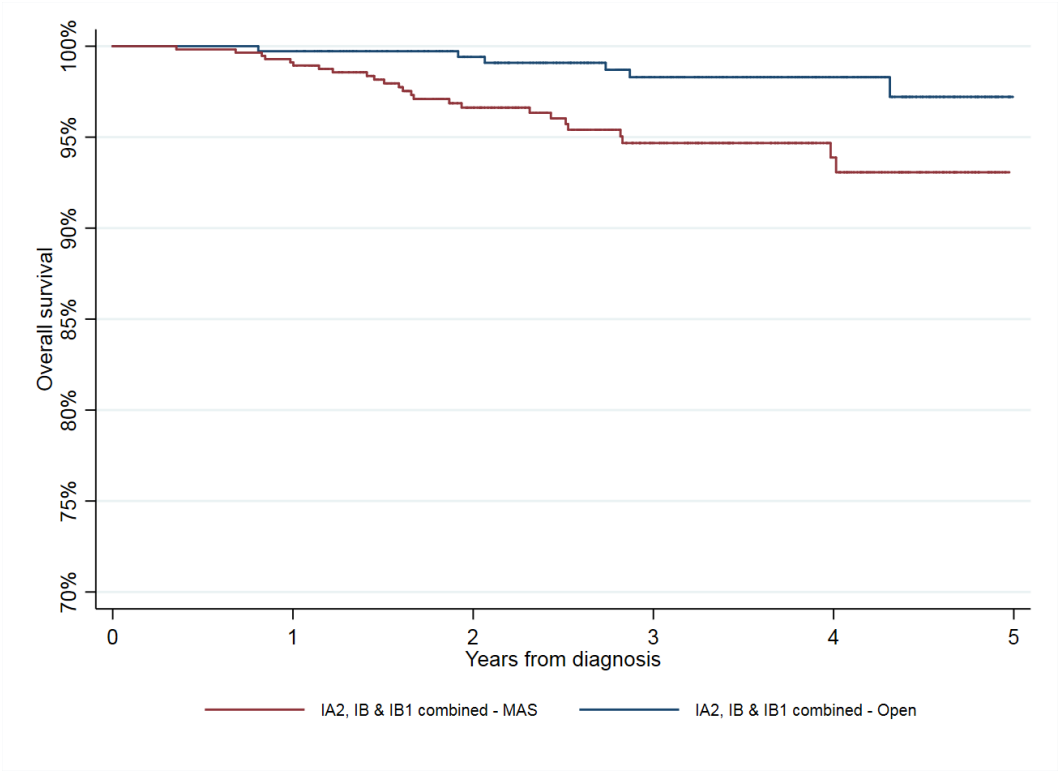
South East	1.9 (1.1 – 3.1)	0.016
South West	1.8 (1.0 – 3.3)	0.044
p-heterogeneity	<0.001	
Adjuvant Chemotherapy		
Yes	0.8 (0.6 – 1.3)	0.403
No	REF	REF
p-heterogeneity	0.403	
Diagnostic route		
Screening	REF	REF
EP	2.2 (0.4 – 13.8)	0.388
Planned referrals (TWW, GP referral, inpatient elective, other outpatient)	1.0 (0.7 – 1.3)	0.845
Unknown	2.7 (0.7 – 9.5)	0.134
p-heterogeneity	0.340	

**P-values from Wald tests*

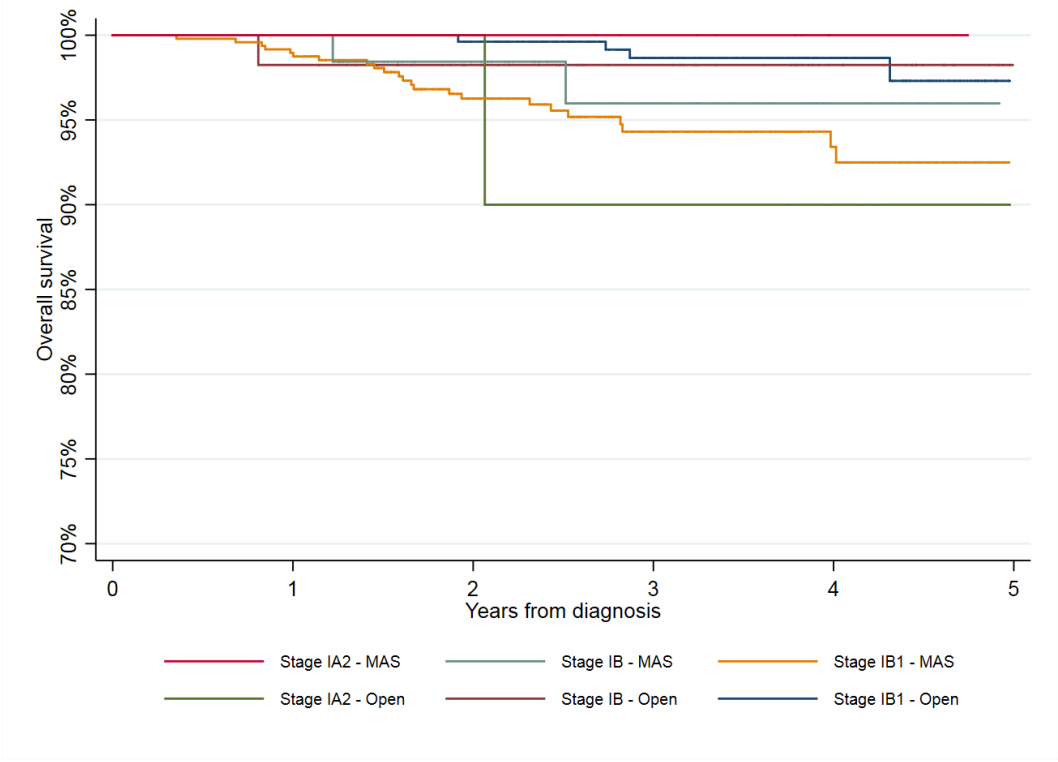
†All variables were further tested for heterogeneity, linearity and non-linearity. No variables required polynomial transformation.

3. Unadjusted analysis, using Kaplan Meier curve / estimators

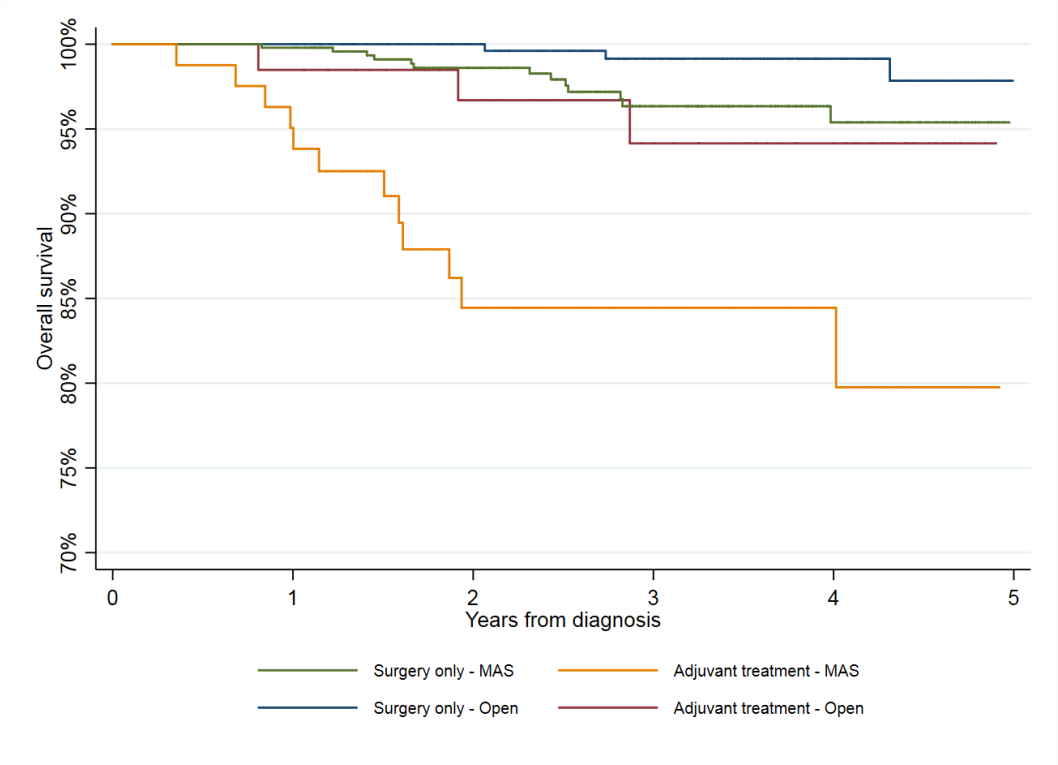
- MAS/open – all patients in either group



- MAS/open groups by early stage group



- MAS/open groups by adjuvant treatment status



3b. Unadjusted analysis, using Kaplan Meier curve / estimators, whereby MAS-converted-to-Open are treated as members of the MAS group as opposed to open group as in main analysis (n= 10 for MAS-converted-to-open group) produced highly similar findings (not shown). It should be noted that no deaths had occurred during follow-up in this small group.

3c. Overall survival at 3m, 6m, 1y, 2y, 3y, 4y, 4.5y

	3 months	6 months	1 year	2 years	3 years	4 years	4½ years
MAS survival	100.0%	99.8% (98.8-100.0)	99.1% (97.9-99.6)	96.6% (94.6-97.9)	94.7% (92.0-96.5)	93.9% (90.6-96.1)	93.1% (89.2-95.6)
Open survival	100.0%	100.0%	99.7% (98.1-100.0)	99.4% (97.7-99.9)	98.3% (95.9-99.3)	98.3 % (95.9-99.3)	97.2% (93.0-98.9)
p-value	n/a	n/a	0.583	0.081	0.111	0.028	0.007

4. Cox regression analysis

4a. Crude models for associations with observed survival for all variables in the table above.

Cox (Univariate)	Hazard Ratio (95% CI)	p-value*
Treatment Type		
Open Surgery	REF	REF
MAS	3.3 (1.4 – 8.1)	0.009

Cox (Univariate)	Hazard Ratio (95% CI)	p-value*
Diagnosis Year		
2013	REF	REF
2014	1.2 (0.8 – 1.7)	0.406
2015	0.8 (0.5 – 1.3)	0.419
2016	0.6 (0.3 – 1.0)	0.065

Cox (Univariate)	Hazard Ratio (95% CI)	p-value*
Age Group		
<30	REF	REF
30-39	0.7 (0.4 – 1.3)	0.311
40-49	0.9 (0.5 – 1.6)	0.617
50-59	1.5 (0.8 – 2.9)	0.170
60+	7.3 (4.5 – 11.9)	<0.001

Cox (Univariate)†	Hazard Ratio (95% CI)	p-value*
Deprivation		
Least Deprived - 1	REF	REF
2	1.1 (0.6 – 2.0)	0.663
3	1.3 (0.8 – 2.3)	0.296
4	1.2 (0.7 – 2.1)	0.466
5	1.2 (0.7 – 2.1)	0.416

Cox (Univariate)†	Hazard Ratio (95% CI)	p-value*
Stage		
IB1	REF	REF
IB	2.3 (1.7 – 3.2)	< 0.001
1A2	1.0 (0.5 – 2.0)	0.927

Cox (Univariate)†	Hazard Ratio (95% CI)	p-value*
Charlson		
0	REF	REF
1	2.5 (1.5 – 4.2)	< 0.001
2+	8.3 (5.6 – 12.3)	< 0.001

Cox (Univariate)†	Hazard Ratio (95% CI)	p-value*
Region		
North West	REF	REF
North East	0.6 (0.3 – 1.5)	0.308
Yorkshire and The Humber	1.0 (0.5 – 1.8)	0.995
East Midlands	1.2 (0.7 – 2.1)	0.456
West Midlands	0.7 (0.3 – 1.3)	0.232
East of England	0.4 (0.2 – 0.9)	0.026
London	0.6 (0.3 – 1.1)	0.108
South East	1.2 (0.7 – 2.0)	0.470
South West	1.1 (0.6 – 1.9)	0.762

Cox (Univariate)†	Hazard Ratio (95% CI)	p-value*
Adjuvant Chemotherapy		
Yes	1.9 (1.1 – 3.2)	0.021
No	REF	REF

Cox (Univariate)†	Hazard Ratio (95% CI)	p-value*
Diagnostic route		
Screening	REF	REF
EP	21.8 (11.2 – 42.7)	<0.001
Planned referrals (TWW, GP referral, inpatient elective, other outpatient)	5.2 (3.3 – 8.1)	<0.001
Unknown	2.8 (0.9 – 9.5)	0.090

4b. Multivariate Cox model (adjusted for case-mix variables) †

Complete Data:

	Hazard Ratio (95% CI)	**p-value***
Surgery Type		
Open	REF	REF
Laparoscopic	4.0 (1.5 – 11.1)	0.007
p-heterogeneity	0.013	
Diagnosis Year		
2013	REF	REF
2014	2.6 (1.0 – 6.9)	0.059
2015	0.9 (0.3 – 3.1)	0.888
2016	#	#
p-heterogeneity	0.016	
Age Group		
<30	REF	REF
30-39	0.2 (0.1 – 0.7)	0.011
40-49	0.1 (0.0 – 0.4)	0.001
50-59	0.3 (0.1 – 1.2)	0.100
60+	0.6 (0.2 – 2.2)	0.469
p-heterogeneity	0.081	
Deprivation		
Least Deprived - 1	REF	REF
2	1.1 (0.3 – 4.2)	0.903
3	0.9 (0.2 – 3.5)	0.872
4	0.7 (0.2 – 3.2)	0.688
Most Deprived - 5	0.6 (0.1 – 2.4)	0.463
p-heterogeneity	0.876	
Charlson		
0	REF	REF
1	1.3 (0.3 – 6.3)	0.740
2+	20.8 (5.1 – 84.8)	< 0.001
p-heterogeneity	0.004	
Stage		
IB1	REF	REF
IB	0.9 (0.2 – 3.6)	0.885
1A2	2.4 (0.3 – 21.2)	0.418
p-heterogeneity	0.901	
Region		
North West	REF	REF
North East	1.6 (0.2 – 15.8)	0.704

Yorkshire and The Humber	1.8 (0.4 – 7.5)	0.404
East Midlands	0.6 (0.1 – 3.5)	0.585
West Midlands	0.3 (0.1 – 1.6)	0.157
East of England	#	#
London	3.0 (0.6 – 15.2)	0.182
South East	2.4 (0.7 – 8.4)	0.164
South West	1.2 (0.2 – 7.1)	0.822
p-heterogeneity	0.060	
Adjuvant Chemotherapy		
Yes	6.8 (2.9 – 16.2)	< 0.001
No	REF	REF
p-heterogeneity	< 0.001	
Diagnostic route		
Screening	REF	REF
EP	#	#
Planned referrals (TWW, GP referral, inpatient elective, other outpatient)	2.4 (1.0 – 5.9)	0.047
Unknown	#	#
p-heterogeneity	0.087	

**P-values from Wald tests*

†All variables were further tested for heterogeneity, linearity and non-linearity. No variables required a polynomial transformation.

#Omitted due to limited data resulting in volatile estimates.

The above model was repeated by including time varying effects for adjuvant therapy status (given statistical evidence for such effects); doing so resulted in immaterial only changes in hazard ratio estimates for all other fixed effect variables (including for MAS vs open approach variable).