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Chand, M, Rasheed, S, Heald, R et al. (5 more authors) (2017) Adjuvant chemotherapy may improve disease-free survival in patients with rectal cancer positive for MRI-detected extramural venous invasion following chemoradiation. Colorectal Disease, 19 (6). pp. 537-543. ISSN 1462-8910

https://doi.org/10.1111/codi.13535

Original article:

Adjuvant chemotherapy may improve disease-free survival in patients with persistently mrEMVI-positive rectal cancer following chemoradiation

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Funding – NIHR BRC Programme Grant

Acknowledgements – nil

Conflict of interests - nil

Abstract

Introduction

MRI-detected extramural venous invasion (mrEMVI) is a poor prognostic factor in rectal cancer. Pre-operative chemoradiotherapy (CRT) can cause regression in the severity of EMVI and subsequently improve survival outcome whereas persistent mrEMVI confers an increased risk of disease recurrence. The effect of adjuvant chemotherapy (AC) following CRT on survival outcomes in rectal cancer remains unclear. The aim of this study was to determine if a survival advantage from AC is observed in patients with persistent mrEMVI following treatment with CRT.

Methods

A prospective analysis was conducted of consecutive patients with locally-advanced rectal cancer between 2006-2013. All patients underwent CRT followed by surgery. AC was given to selected patients based on the presence of specific 'high-risk' features. Comparison was made between patients offered AC with observation alone. The primary outcome measure was 3-year disease-free survival (DFS).

Results

227 patients of 631(36.0%) demonstrated persistent mrEMVI following CRT. Patients were grouped on the basis of AC or observation and matched for age, performance status and final pathological staging. 3-year DFS in the AC group was 74.6% compared to 53.7%. AC had a survival benefit on multivariate analysis (HR 0.458; 95%CI 0.271-0.775 p=0.004).

Conclusion

Patients with evidence of persistent mrEMVI who receive AC following CRT may have a decreased risk of disease recurrence and improved 3-year DFS, independent of age and performance status.

What does this paper add to the literature?

This paper provides further evidence that MRI-detected EMVI is associated with poor prognosis in rectal cancer. Further, it is shown to be a treatment consideration and should be respected in decisions regarding adjuvant chemotherapy where current consensus is lacking.

Introduction

MRI-detected extramural venous invasion (mrEMVI) is a poor prognostic factor in rectal cancer associated with adverse survival outcomes (1, 2). Persistent mrEMVI following pre-operative chemoradiotherapy (CRT) has been shown to have an increased risk of disease recurrence (3-5) – Figure 1. Conversely, when there is radiological evidence of fibrosis within the extramural veins and regression of venous disease, the survival outcomes of patients are improved (6) suggesting that patients with persistent mrEMVI represent a 'high-risk' group - stage II tumours which demonstrate EMVI have been previously shown to have similar survival outcomes as stage III tumours following CRT (7).

The role and timing of adjuvant chemotherapy in rectal cancer remains contentious and the evidence-base is lacking compared to colon cancer (8). The QUASAR trial (9) still provides the only robust evidence for the use of adjuvant chemotherapy in rectal cancer albeit this is limited compared to colonic cancer. Furthermore, the effect of adjuvant chemotherapy for patients who have already undergone CRT is even less clear.

Adjuvant chemotherapy remains the main oncological treatment to improve long-term survival although its optimal timing and which patients are most likely to benefit is still not clear. The aim of this study was to determine if a survival advantage from adjuvant chemotherapy is observed in patients with persistent mrEMVI following CRT.

Methods

Patients and ethics

Patients were identified from a prospectively maintained database. Data was extracted on consecutive patients undergoing curative treatment for locally advanced rectal cancer between January 2006 and January 2013. Treatment included long-course neoadjuvant chemoradiotherapy followed by surgery. Adjuvant chemotherapy was offered to selected patients based on the presence or absence of specific adverse or 'high-risk' features (nodal disease, increasing tumour penetration into the mesorectum, threat of the circumferential resection margin) following an informed discussion. Patients with synchronous tumours, undergoing local excision and those treated with palliative surgery were excluded. There was central review of all pathology and radiology by specialised GI pathologists and radiologists, respectively.

This study was carried out following internal review of the study proposal by the Department of Clinical Research and Development at The Royal Marsden Hospital.

Staging and neoadjuvant therapy

All patients were staged by complete clinical examination which included colonoscopy, high-resolution magnetic resonance imaging (MRI) scan of the rectum and computed tomography (CT) scan of the thorax, abdomen and pelvis. All treatment decisions were made as part of a multidisciplinary team meeting. Our policy has been to offer long-course pre-operative chemoradiotherapy (54Gy in fractions with concominant 5-fluorouracil based chemotherapy) to patients with any of the following criteria: tumour within 1 millimetre (mm) of the mesorectal fascia or bordering the intersphincteric plane (potential circumferential resection margin involvement), MRI detected EMVI, extramural tumour spread >5mm, and N2 nodal disease (metastasis in 4 or more

regional lymph nodes). Patients were fully restaged with MRI following completion of pre-operative therapy. These restaging MRIs were used to determine the presence of persistence EMVI and formed the basis of patient grouping for analysis.

Adjuvant chemotherapy regime

The decision to offer patients chemotherapy following surgery was made during the multidisciplinary meeting. Not all patients were offered the same regime and this was determined following informed discussion. No regime lasted longer than 6 months unless there was progression of disease with a view towards palliation. The regimes can be divided into i) Capecitabine; ii) Capecitabine and Oxaliplatin; iii) 5-FU based; iv) Folinic acid, 5-FU and Oxaliplatin; v) Other. All adjuvant treatment was started within 6 weeks of surgery.

Outcome measures

The primary outcome was 3-year disease-free survival from the date of surgery. The main secondary outcome was recurrence rate. A recurrence was defined by radiological or histological evidence of disease and confirmed on multidisciplinary discussion.

Definitions

Performance status was defined according to the Eastern Cooperative Oncology Group (ECOG) classification. Evidence of mrEMVI was confirmed on T2-weighted images and seen as serpiginous or tortuous linear structures. Assessment of mrEMVI included the following: pattern of tumour margin (extension into small veins may produce a nodular border); location of tumour relative to major vessels; vessel calibre

(tumour causes vessel expansion and increase in tumour signal in the lumen); and vessel border. Smaller venules can be seen perforating the normal outer rectal wall and produce a low to intermediate signal intensity in tubular structures on T2-weighted images. Venous invasion into these smaller venules can be seen recognised by their expansion and irregularity adjacent to the tumour due to contiguous tumour extension. A positive resection margin was defined as tumour within 1mm of the circumferential resection margin. Staging was performed according the 5th Edition of the Tumour, Node, Metastasis (TNM) system from the American Joint Committee on Cancer and was based on final pathological findings. Stages II disease is classified as T1-4, N0, M0 and stage III as T1-4, N1-2, M0. Disease free survival (DFS) was the time from the date of surgery to the date of pelvic recurrence and/or distant disease or death due to pelvic recurrence and/or distant disease.

Statistical analysis

Differences between groups were assessed using the Chi-squared test or Fisher's Exact test as appropriate. Survival estimates for DFS were obtained using the Kaplan-Meier product limit method. Patients were censored at the last point of known contact or if they died during follow-up without experiencing the outcomes of interest.

Cox's proportional hazard models were built to test the impact of confounding variables on survival (age, gender, performance status, pathological T-stage and N stage, CRM involvement). These models allow the effect of predictive factors on outcome to be assessed, accounting for censored outcome, differing time of follow-up, and the interval between surgery and the adverse event of interest. Hazard ratios (HR) and 95% confidence intervals (CI) were generated. In order to provide clinically and meaningful risk adjustment, a fully adjusted model was used – all predictive risk

factors that were judged to be clinically relevant were entered into a fixed model to adjust the impact of adjuvant chemotherapy on survival. Data were analysed using SPSS 21 (SPSS Inc, Chicago, Illinois) and Excel 2013.

Results

Demographics and treatment

A total of 227 of 631 (36.0%) had evidence of persistent mrEMVI following CRT. The median age was 63.5 (IQR: 54.8- 72). 158 patients had undergone adjuvant chemotherapy with 69 being observed following surgery. Demographic and tumour characteristics are shown in table 1.

Histopathology staging characteristics

The majority of patients had advanced disease – T stage 3 and 4. However nodal disease was less common with less than third showing histopathological evidence of malignant nodes following CRT. Only 14 patients (6.2%) had a positive CRM after surgery.

Comparison of adjuvant chemotherapy and observation groups

Patients were grouped into whether or not they had received adjuvant chemotherapy. Demographic and tumour characteristics are shown in table 3. Both groups were matched in terms of age, performance status and final pathological staging characteristics (T and N stage, and CRM status). The majority of patients in both groups were of performance status 0 or 1 (n = 206; 90.7%); and had locally advanced disease in terms of T-stage. Table 4 shows the different chemotherapy regime offered to patients.

Survival analysis

At a median follow-up of 26 months (2-84) there were 68 recurrences of which 12 (17.6%) were local recurrences. In the AC group there were 10 local and 34 distant recurrences. In the observation group there were 2 local and 22 distant recurrences.

The 3 year DFS for patients that received adjuvant chemotherapy was 74.6% and observation only 53.7% (Graph 1). There was a significant difference in disease-free survival using Mantel Cox Log Rank Test – p=0.02. On multivariate analysis, CRM involvement was a significant factor for reduced 3 year DFS (HR 3.891; 95%CI 1.642-9.174).

For the purposes of analysis, patients who received adjuvant chemotherapy were used as reference to test the significance of chemotherapy on disease recurrence. Adjuvant chemotherapy had a survival benefit on multivariate analysis (HR 0.458; 95%CI 0.271-0.775). The full results are seen in table 3.

Discussion

The main finding of the present study is that patients with persistent mrEMVI who receive adjuvant chemotherapy following neoadjuvant chemoradiation had a reduced risk of developing disease recurrence. This was independent of age, performance status and nodal disease. These patients also had a significantly improved disease-free survival at 3 years compared to patients undergoing clinical follow-up alone (74.6% versus 53.7%). Although the majority of patients in the study had adjuvant chemotherapy, approximately 30% did not implying there is a significant number of patients who may benefit from additional treatment but are currently being denied optimal treatment. It is notable that nodal disease was not an independent factor for disease recurrence in matched patients who have previously undergone neo-adjuvant treatment and oncologically successful surgery. CRM status was also shown to be a significant factor for disease relapse.

There is a lack of consensus on the use of adjuvant chemotherapy following neo-adjuvant chemoradiation (8, 10). The current European and North American guidelines recommend that all patients with stage III and ‘high-risk’ stage II rectal cancers are offered adjuvant chemotherapy although this is not underpinned by a robust evidence base. However, the survival benefit of further treatment with up to six months of 5-FU-based chemotherapy in patients who may have already had a significant response from pre-operative treatment is unknown and further confuses the issue. The literature shows that patients who have had minimal response from neoadjuvant treatment demonstrate no survival benefit following adjuvant chemotherapy (11-13). The PROCTOR/SCRIPT trial is a Dutch-Swedish collaborative phase III study of patients with stage II or III rectal cancer who have undergone pre-operative CRT and surgery.

Comparison was made between those patients having adjuvant chemotherapy and those under observation only. A total of 437 patients were eligible for analysis with a median follow-up of 5 years. There was no difference in DFS, overall survival (OS) or recurrence rates (14). Bosset et al, have recently published long-term outcomes from the well-known EORTC Trial 22921. In this study, patients with T3 or T4 disease were assigned to chemotherapy or observation following pre-operative radiotherapy (with or without sensitising chemotherapy). Again, there was no difference in terms of DFS and OS at median follow up of 10.4 years. A recent meta-analysis also showed no survival benefit in patients with stage II and III disease following CRT – this included DFS and OS (15). This would suggest that the results of the present study are at odds with the literature. However, the present study is not directly comparable and instead highlights the difficulty in conducting trials involving adjuvant chemotherapy.

This study has investigated a specific high-risk factor rather than analysing outcomes from all patients who have undergone pre-operative treatment. The DFS of the observation group is much lower than those studies which have looked at more general outcomes but this simply demonstrates the high likelihood of recurrent or metastatic disease in patients with persistent EMVI. Previous studies have shown the increased risk of disease recurrence with EMVI (4, 7, 16) so it is not surprising that patients with persistent mrEMVI who are undergo observation only have a significant risk of developing metastases.

Risk stratification has evolved in recent years and the use of MRI in this area has become increasingly popular. The published evidence does not account for patients selected for analysis on MRI-based associated features which we now know are important determinants of prognosis (16, 17). This is an area which requires further study and robust randomised trial evidence to determine which patients will most

benefit from adjuvant chemotherapy as increasing numbers are undergoing ‘successful’ pre-operative treatment. A ‘blanket’ approach whereby all patients are routinely given adjuvant therapy may potentially lead to substantial over-treatment with perhaps no additional survival benefit. The use of MRI in selecting high-risk patients may further improve future trial design allowing for treatment decisions to be made in conjunction with pathology.

This uncertainty has led to a variability in practise with regards to adjuvant chemotherapy decisions amongst clinicians (18). Khrizman et al, have explored the reasons behind the variability in adjuvant chemotherapy use and whether this is related to patient or tumour characteristics (19). They found that age, co-morbidity (performance status), operative complications and complete pathologic response were significant factors for not receiving adjuvant chemotherapy. Age is most commonly cited as a reason for not recommending or offering adjuvant treatment (20-22) however there is good evidence to show comparable outcomes for elderly patients who are given such treatment in both colon and rectal cancer (23, 24). With an increasing elderly population and a drive towards improving outcomes for this group of patients, we will no doubt see a rise in the number of elderly patients being offered adjuvant treatment in the future. Another interesting point is that co-morbidity or performance status which are often used as reasons why eligible patients did not receive adjuvant chemotherapy (25). Patients have already been through both neo-adjuvant treatment and major surgery which means that unless it is the initial treatment that has led to a decrease in performance status, this factor becomes redundant.

The design of the present study and the subsequent analysis attempted to address some of these points which have previously explained the variability in practise with regards to adjuvant chemotherapy. We consider mrEMVI to be a ‘high-risk’ factor and

that patients should be offered adjuvant treatment to reduce the risk of disease recurrence. Whilst there are many reasons for patients to be offered or declined chemotherapy, the patients in the study were matched in terms of age, performance status and final staging which means the results of the multivariate analysis show a true independence for disease recurrence. All patients received the same staging and treatment apart from subtle variation in the specific adjuvant chemotherapy regime.

mrEMVI is being increasingly recognised as a prognostic factor (4, 7, 26). This radiological characteristic has been shown to be affected by neoadjuvant treatment and in those patients where there has been a significant response there is an associated improvement in survival outcomes; thus being proposed as an imaging biomarker in rectal cancer in initial small-scale study (6). There have been recent concerns regarding the reliance on routine pathological analysis to accurately detect EMVI particular after CRT when much of the architectural features which form the basis of identification are lost by the fibrosing effect of CRT (27). Using radiological characteristics to guide and inform adjuvant treatment decision-making is becoming more popular and is already universally done so with regards to neoadjuvant treatment. Extending this to adjuvant treatment seems a natural progression particularly if there is difficulty in interpreting routine pathological analysis following CRT and there is a potential for patients who may benefit from further treatment to be missed.

Limitations of the study include a lack of information regarding the decision-making process following surgery. Knowledge of whether treatment was not recommended or whether not offered would have given further understanding to any variability in practise. Also, there was no information regarding severity and extent of any operative complications. This is known to be a factor in delaying or withholding adjuvant

treatment and may have played a role in this study. Understandably, if a patient has endured a challenging journey through the first phases of their treatment they are less likely to consider further therapy particularly if there is a risk of morbidity. Furthermore, to quantify the effect of adjuvant chemotherapy most accurately the ideal study design is a randomized prospective study with a larger number of patients. The present retrospective study will inherently contain some selection bias when it comes to which patients were offered chemotherapy although the matching of the two group goes some way to mitigate for this. A further limitation is the primary outcome measure of using DFS does not account for death from other causes. This confoucnding factor has the potential to bias the results although in these numbers that likelihood is small and 3-year DFS is widely considered a good measure of survival outcome.

This study has provided further evidence that there may be selected patients who will benefit from adjuvant treatment. It is also the first study to use MRI to select patients deemed ‘high-risk’ meaning that decisions to intensify treatment can be tailored before surgery when compliance and effect may be improved although the numbers are small to make definitive recommendations on chemotherapy use in this context.

Figure 1 – MRI sections showing EMVI following treatment with chemoradiation. The red arrows show the precise location of the extramural veins containing tumour signal.

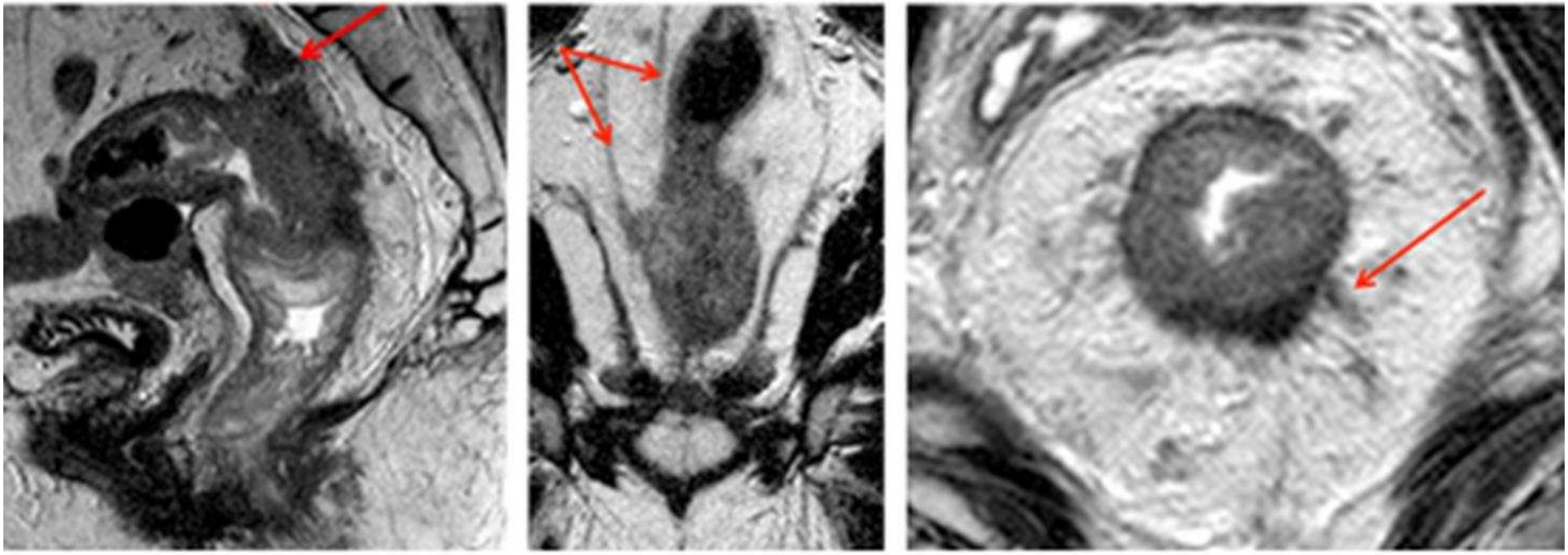

Table 1 - Cohort characteristics split by the adjuvant chemotherapy

		Adjuvant chemotherapy *N (%)*	**Observation** *n (%)*	**Total**	**P-value**
Age	<70	98 (62)	48 (70)	146	
	>70	60 (38)	21 (30)	81	0.30
Performance status	0-1	144 (91)	62 (90)	206	
	2-3	14 (9)	7 (10)	21	0.14
Gender	Female	45 (28)	28 (41)	73	
	Male	113 (72)	41 (59)	154	0.09
Pathological T-stage	T0-2	32 (20)	19 (28)	51	
	T3-4	126 (80)	50 (72)	176	0.34
Nodal status	Negative	110 (70)	48 (70)	158	
	Positive	48 (30)	21 (30)	69	0.95

Table 2 – Drugs used in Adjuvant chemotherapy

No of patients	**Capecitabine**	**Capecitabine and Oxaloplatin**	**5-FU only**	**FOLFOX**	**Other**
Total (n=144)	47	34	6	45	12

Graph 1 – Kaplin Meier Curves showing Disease-Free Survival

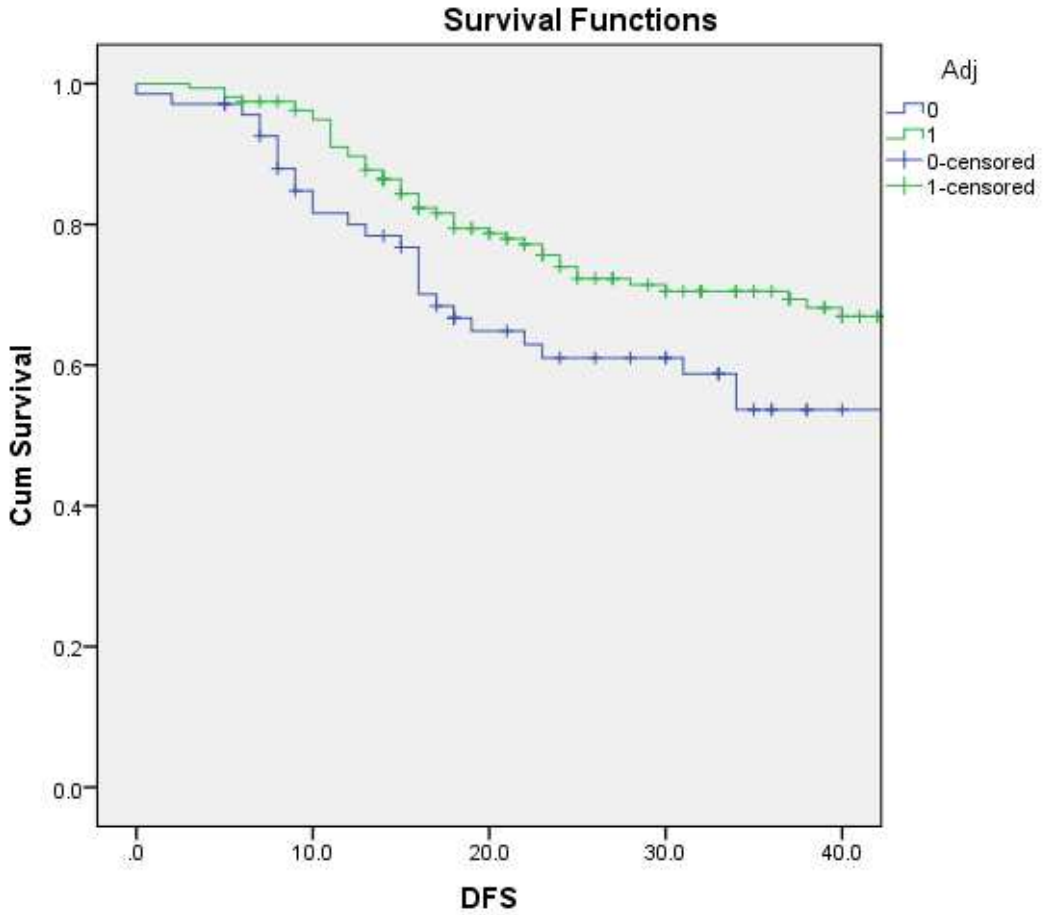

Table 3 - Fully adjusted multivariable Cox's proportional hazard models for 3 year DFS

		HR	95% CI lower	95% CI upper	P value
Gender	Female	Ref			
	Male	1.125	0.668	1.895	0.657
Pathological T-stage	T0	Ref			
	T1	1.633	.234	5.048	.914
	T2	.822	.217	18.302	.543
	T3	2.571	.210	3.508	.831
	T4	1.270	.940	6.951	.066
Pathological N-stage	Negative	Ref			
	Positive	1.372	0.799	2.353	.252
CRM	Negative	Ref			
	Positive	3.891	1.642	9.174	0.02
Performance status	0	Ref			
	1	1.837	.518	.146	.309
	2	1.376	.393	.112	.144
	3	2.085	.488	.114	.333
Adjuvant chemotherapy	No	Ref			
	Yes	0.458	0.271	0.775	.004
pEMVI	Negative	Ref			
	Positive	2.041	1.168	3.559	.012
Age	Below 70	Ref			
	Above 70	0.997	0.975	1.019	.765

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