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Site and stage of colorectal cancer influence the likelihood and distribution of disease recurrence and post recurrence survival – data from the FACS Randomised Controlled Trial

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Type of study: Retrospective cohort analysis of randomised controlled trial data

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Running head: Analysis of recurrence in the FACS study

Mini Abstract

Recurrence is a frequent cause of mortality following treatment for colorectal cancer with curative intent. This retrospective cohort analysis examines patterns of recurrence, and factors determining post-recurrence survival, in a large cohort of accurately staged patients treated curatively for Dukes' A-C primary colorectal cancer from the FACS randomised controlled trial.

Structured Abstract

Objective

To describe patterns of recurrence and post-recurrence survival (PRS) in a large cohort of accurately staged patients with Dukes' A-C colorectal cancer (CRC).

Background

Recurrence remains a frequent cause of mortality following the treatment of CRC with curative intent. Understanding the likelihood and site of recurrence informs adjuvant treatment and follow-up.

Methods

Retrospective cohort analysis of data from the FACS (Follow-up after Colorectal Cancer Surgery) trial after a median 4.4 years follow-up; PRS was calculated using the Kaplan-Meier method.

Results

Complete data were available for 94% of patients; 189 (17%) had experienced recurrence. Incidence of recurrence varied according to the site of the primary (right colon: 51/379, 14%; left colon: 68/421, 16%; rectum: 70/332, 21%; p=0.023) and initial stage (Dukes' A: 26/249, 10%; Dukes' B: 81/537, 15%; Dukes' C: 82/346, 24%; p<0.0001). Pulmonary recurrence was most frequently associated with rectal tumors, and multi-site/other recurrence with right-colonic tumors. Recurrences from lower stage tumors were more likely to be treatable with curative intent (Dukes' A: 13/26, 50%; Dukes' B 32/81, 40%; Dukes' C 20/82, 24%; p=0.03). Those with rectal tumors benefited most from follow-up (proportion with treatable recurrence: rectum 30/332, 9%; left colon 23/421, 6%; right colon 12/379, 3%; p = 0.003). Both initial stage (log rank p = 0.005) and site of primary (log rank p = 0.01) influenced PRS.

Conclusion

The likelihood and site of recurrence, as well as survival, are influenced by the site and stage of the primary tumor. Those with rectal cancers benefited most from follow-up.

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INTRODUCTION

Recurrence remains a frequent cause of mortality following the surgical treatment of colorectal cancer with curative intent. Understanding both the likelihood and site of recurrence is important for planning optimal adjuvant treatment and follow-up. For example, rectal cancer has a well-established tendency to recur locally; however, the combination of total mesorectal excision and optimal chemoradiotherapy has reduced rates to less than 10% in modern series.[1-4] Existing evidence on the pattern of recurrence after curative resection of colorectal cancer is limited to retrospective audits[5-7] and data from high quality randomised controlled trials is lacking. Trials of adjuvant therapies for colon and rectal cancer reveal certain information on patterns of recurrence but these are by definition limited to more advanced stage cancers requiring such treatments.[8]

Surgical resection of both metastatic and locally recurrent disease is now widely practiced with a good proportion of patients enjoying long-term survival.[9-11] These meta-analyses report prognostic features for survival following recurrence; however, they include patients with both synchronous and non-synchronous presentations and the disease biology may be different. Furthermore, the prognostic factors identified typically relate to observations at the time advanced disease is identified, such as number and size of metastatic lesions, and carcinoembryonic (CEA) antigen level,[10, 11] with less emphasis placed on characteristics of the primary tumor.

The FACS (Follow-up after Colorectal Cancer Surgery) trial data therefore provide an important opportunity to refine our understanding of the prognostic significance of initial site and stage on the frequency and site of recurrence. One of the key findings of the trial was the low overall incidence of recurrence, thought to be due to the rigour of the investigative procedures undertaken to ensure that no residual disease was present at trial entry.[12] As such this affords a unique population of patients with colorectal cancer surgically treated with

curative intent, both accurately staged and prospectively followed-up, in which to analyse patterns of disease recurrence and factors influencing post recurrence survival.

METHODS

A total of 1202 patients were recruited to the UK FACS trial between January 2003 and August 2009; this analysis is restricted to 1132 patients (94.2%) for whom complete detailed data are available on initial stage and site of recurrence. The cut-off date for this analysis is 31 August 2012 by which time all patients had reached a minimum of three years of follow-up, with a median follow-up of 4.4 years since randomisation.

All FACS trial participants had undergone curative treatment for primary colorectal cancer, Dukes' A-C staging (TNM Stage I-III), with microscopically clear margins. All were disease-free on colonic imaging with no evidence of metastatic disease (CT chest abdomen pelvis +/- MRI liver) and with a post-operative blood CEA 10µg/ml or less. For those receiving adjuvant therapy the CEA was measured at completion of treatment and a CT performed. Patients were randomised using a factorial 2x2 randomised design from 41 centres in the UK to 6-12 monthly CT imaging or minimum follow-up and to 3-6 monthly CEA testing or minimum follow-up; details of the design, conduct, and results of this clinical trial are available in the original publication.[12] This retrospective cohort analysis aggregates data from all four trial arms.

Information on deaths was collected by flagging each participant at the ONS central registry; as all patients who withdrew from the study gave permission for continuation of flagging, the mortality follow-up is complete except for one patient who has emigrated. Cause of death was abstracted from death certificates; in some cases clinical records were consulted to investigate further the role of colorectal cancer as an important contributory cause of death. Data on treatment of recurrence and treatment intent were abstracted from the hospital records by the local NIHR cancer network nurse and collated by the data manager in Oxford;

these data were reviewed independently by the chief clinical investigators (blind to allocation group) to check for consistency and where necessary further information was sought from the relevant clinical teams to resolve any clinical ambiguity. The final decision on treatment intent was made at a review meeting with independent clinical input.

Categorical variables are presented as frequencies (percentages) and the chi-square test used for comparisons. The Kaplan-Meier method was utilised for survival analyses and the log-rank test used to compare survival between groups; $p<0.05$ was considered significant. Tables were produced using SPSS statistical software version 22 (IBM Corp, NY) and survival analyses were carried out using the 'survival' package in R (R Development Core Team, 2014).

RESULTS

Incidence of recurrence

Within the median follow-up period of 4.4 years (IQR: 3.1-5.0 years), 189 participants (17%) developed recurrence. The mean age of participants with recurrence was 67.8 years and 63% were male (table 1). The incidence of recurrence varied according to the site of the original tumor. Recurrence was detected in 14% (51/379) participants with a right-colonic primary tumor, 16% (68/421) with a left-colonic primary tumor and 21% (70/332) with a primary tumor in the rectum ($p=0.023$) (table 2). Predictably, recurrence was more frequent in those with a more advanced stage primary tumor; 10% of participants with a Dukes' A primary tumor developed recurrence (26/249), compared to 15% (81/537) with a Dukes' B and 24% (82/346) with a Dukes' C primary tumor ($p<0.0001$) (table 2).

Site of recurrence

Of the 189 participants with recurrence, single site recurrence in the liver, lung or locally was present in 124 (liver=50, lung=33 and locoregional=41), with the remainder having recurrence at other or multiple sites. Overall the liver was the most frequent site of

recurrence, with 42% (79/189) of all recurrences involving the liver. Interestingly, the distribution of recurrent disease varied according to the location of the primary tumor. Recurrence involving just the lung was most frequently associated with primary tumors in the rectum (right colon=3/33, 9%; left colon=8/33, 24%; rectum=22/33, 67%; p<0.0001). In addition, recurrence at sites other than the lung, liver or locoregionally, or at more than one of those sites were most likely to be experienced by those with right colonic primary tumors (right colon=25/65, 38%; left colon=23/65, 35%; rectum=17/65, 26%; p = 0.018). Site of recurrence was also influenced by the stage of primary tumor; both locoregional recurrence and recurrence at multiple/other sites was most frequently associated with higher stage primary tumors (see table 2).

Incidence of recurrent disease treatable surgically with curative intent

Of the 189 participants with recurrence, a total of 65 (34%) underwent treatment with curative intent (table 3). Those participants with recurrence and a lower stage original tumor were more likely to be resectable (Dukes' A 13/26, 50%; Dukes' B 32/81, 40%; Dukes' C 20/82, 24%; p=0.08). While there was no significant difference in the likelihood of recurrent disease being amenable to curative resection according to the site of original tumor, a trend was apparent (right colon: 12/51, 24 %; left colon: 23/68, 34 %; rectum: 30/70, 43 %; p=0.086).

Benefit of follow up

Although recurrent disease was more likely to be resectable in those with a lower stage primary tumor, the proportion of participants with recurrence surgically treated with curative intent taken as a proportion of the whole trial cohort was similar for each Dukes' stage (A: 13/249, 5%; B 32/537, 6%; C: 20/346, 6%; p=0.80). As such, a key finding of the FACS trial was that the benefit of follow-up is independent of stage - that is, while recurrence is less frequent in those with Dukes' A primary tumors, it is more likely to be treatable.[12] By contrast, the benefit of follow-up did vary according to the site of the primary tumor. Those participants with a rectal primary tumor were more likely to have a treatable recurrence detected during

the follow-up period (right colon: 12/379, 3%; left colon: 23/421, 6%; rectum: 30/332, 9%; p=0.003).

Survival post recurrence

Of the 189 diagnosed with recurrent disease, 113 (60%,106 specifically from recurrence and 7 from other causes) died during the follow-up period. Survival post-recurrence differed according to both the site (log rank p=0.01) and stage (log-rank p=0.005) of the primary tumor (Figures 1A and 1B). When just those participants with recurrence from a Dukes' C primary tumor are considered, there is no difference in post recurrence survival according to site of the original tumor (figure online only). However, for those participants with a Dukes' B primary tumor, the site of original tumor appears to influence post recurrence survival (log rank p=0.002 - figure online only). There were insufficient numbers to make comparisons among those with a Dukes' A primary tumor.

Survival post recurrence also differed according to the site of recurrent disease. Those with multi-site recurrence or metastatic recurrence at other sites had an inferior survival to those with single site recurrence in the liver, lung, or locoregionally (figure 1C, log rank p<0.0001), consistent with the high proportion of patients with these single site recurrences undergoing surgical treatment with curative intent (liver only 30/50, 60%; lung only 13/33, 40%; locoregionally only 16/41, 40%; multi-site/other recurrence 6/65, 9%).

For those amenable to treatment with curative intent, around three-quarters (44/65, 74%) were still alive at the end of the follow-up period. Neither the site nor stage of the primary tumor influenced the survival of those with recurrent disease treated with curative intent, although there was a trend towards worse survival in those with a higher stage primary (figure 2).

DISCUSSION

This is the first study to report patterns of recurrence and post recurrence survival in patients with Dukes' A-C colorectal cancer treated with curative intent in a prospectively followed-up, large cohort of patients. As stated in the introduction, the rigour of investigative procedures undertaken to ensure that patients were free of disease prior to recruitment provided an accurately staged population in which to assess the true incidence of disease recurrence.

As might be expected, the results confirm that recurrent disease is most frequent in those with a more advanced stage primary tumor at original diagnosis, even when the staging to identify postoperative residual disease is done meticulously. They also largely confirm the pattern of recurrence reported by other studies;[6-8] while the liver is the most frequent site of recurrence for both colonic and rectal tumors, there is a preponderance of solitary pulmonary metastasis in those with primary tumors in the rectum. This supports the contention that haematogenous spread via the iliac veins results in a higher incidence of lung metastases from rectal cancer.[13, 14] By contrast, locoregional recurrence of rectal tumors was relatively uncommon and certainly no more frequent than colonic tumors. This is consistent with the modern use of surgical techniques to ensure a complete excision of the mesorectum selectively combined with the use of chemoradiotherapy that has dramatically reduced the rates of locoregional recurrence from rectal cancer.[1-4]

A novel finding from this analysis is the suggestion that multi-site recurrence is more common with right-colonic primary tumors. Furthermore recurrence from a right-colonic primary is less likely to be resectable compared with left-sided tumors. Whereas a key finding of the FACS trial was that the benefit of follow-up was independent of stage, it is not independent of tumor site - almost three times as many participants with a rectal primary tumor had recurrent disease detected that was amenable to treatment with curative intent compared to those with a right-sided colonic tumor.

Differences in the clinical presentation and tumor biology between right and left-sided cancers have long been reported,[15-18] and there is now evidence to suggest that different genetic alterations dominate the pathway to relapse between right and left-sided colonic tumors.[19] Traditionally right-sided tumors are believed to present later and be associated with advanced stage disease at presentation,[20] but worse prognosis for right-sided colonic tumors has only been consistently observed in stage III cancers.[16, 21]Our data show that patients with a right-sided tumor are disadvantaged in terms of post-recurrence survival.

The observation that the Dukes' stage of the primary tumor influenced survival after the development of recurrent disease is in agreement with an analysis of patients with stage II and III disease that had participated in trials of adjuvant chemotherapy.[22] In that analysis stage II patients had a longer survival following tumor recurrence compared to stage III patients. It may be that a higher stage tumor at original diagnosis does not simply reflect a later stage in the developmental pathway of colorectal cancer, but rather a more aggressive tumor type, the prognostic implications of which remain if recurrence occurs.

The site of cancer recurrence also influenced survival post the diagnosis of recurrent disease. It is perhaps unsurprising that those with multi-site recurrence had an inferior survival to those with recurrence at the single sites of liver, lung or locoregionally, particularly when considering the low proportion of these participants that were surgically treatable with curative intent. It is however noteworthy that the survival of those with locoregional only recurrence was comparable to that of liver only and lung only recurrence. This supports the current approach of aggressive surgical management of these patients when possible.

Finally the recently published guidelines on follow-up endorsed by the American Society of Clinical Oncology noted there was insufficient evidence to make any clear recommendations for patients with resected stage I disease.[23] The FACS trial now provides us with unequivocal evidence for undertaking surveillance with either CEA measurements or CT imaging in

patients with Dukes' A-C colorectal cancer.[12] Whilst the benefit of follow-up does differ according to the site of primary colorectal cancer we would still recommend undertaking equivalent surveillance strategies in all patients, accepting that there is simply different disease biology at play. It will however provide valuable information to clinicians counselling individual patients about the relative benefits to them participating in a follow-up strategy.

In conclusion the FACS cohort demonstrates that characteristics of the primary colorectal tumor, specifically site and stage, influence the not only the likelihood of recurrence, but the distribution of recurrent disease and post-recurrence survival. The influence of stage on outcome even post recurrence suggests that the stages of primary colorectal cancer represent different disease biology rather than simply points in the timeline of disease progression.

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References

1. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* 2007; 246:693-701.
2. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; 351:1731-40.
3. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; 355:1114-23.
4. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; 345:638-46.
5. Obrand DI, Gordon PH. Incidence and patterns of recurrence following curative resection for colorectal carcinoma. *Dis Colon Rectum* 1997; 40:15-24.
6. Ding P, Liska D, Tang P, et al. Pulmonary recurrence predominates after combined modality therapy for rectal cancer: an original retrospective study. *Ann Surg* 2012; 256:111-6.
7. Roth ES, Fetzer DT, Barron BJ, et al. Does colon cancer ever metastasize to bone first? a temporal analysis of colorectal cancer progression. *BMC Cancer* 2009; 9:274.
8. Kornmann M, Staib L, Wiegel T, et al. Long-term results of 2 adjuvant trials reveal differences in chemosensitivity and the pattern of metastases between colon cancer and rectal cancer. *Clin Colorectal Cancer* 2013; 12:54-61.
9. Colibaseanu DT, Mathis KL, Abdelsattar ZM, et al. Is curative resection and long-term survival possible for locally re-recurrent colorectal cancer in the pelvis? *Dis Colon Rectum* 2013; 56:14-9.
10. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012; 4:283-301.

11. Gonzalez M, Poncet A, Combescure C, et al. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. *Ann Surg Oncol* 2013; 20:572-9.

12. Primrose JN, Perera R, Gray A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA* 2014; 311:263-70.

13. Tan KK, Lopes Gde L, Jr., Sim R. How uncommon are isolated lung metastases in colorectal cancer? A review from database of 754 patients over 4 years. *J Gastrointest Surg* 2009; 13:642-8.

14. Tepper JE, O'Connell M, Hollis D, et al. Analysis of surgical salvage after failure of primary therapy in rectal cancer: results from Intergroup Study 0114. *J Clin Oncol* 2003; 21:3623-8.

15. Hutchins G, Southward K, Handley K, et al. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. *J Clin Oncol* 2011; 29:1261-70.

16. Benedix F, Kube R, Meyer F, et al. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. *Dis Colon Rectum* 2010; 53:57-64.

17. Glebov OK, Rodriguez LM, Nakahara K, et al. Distinguishing right from left colon by the pattern of gene expression. *Cancer Epidemiol Biomarkers Prev* 2003; 12:755-62.

18. Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. *J Surg Oncol* 2004; 88:261-6.

19. Bauer KM, Hummon AB, Buechler S. Right-side and left-side colon cancer follow different pathways to relapse. *Mol Carcinog* 2012; 51:411-21.

20. Sadahiro S, Suzuki T, Ishikawa K, et al. Recurrence patterns after curative resection of colorectal cancer in patients followed for a minimum of ten years. *Hepatogastroenterology* 2003; 50:1362-6.

21. Weiss JM, Pfau PR, O'Connor ES, et al. Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results--Medicare data. *J Clin Oncol* 2011; 29:4401-9.

22. O'Connell MJ, Campbell ME, Goldberg RM, et al. Survival following recurrence in stage II and III colon cancer: findings from the ACCENT data set. *J Clin Oncol* 2008; 26:2336-41.

23. Meyerhardt JA, Mangu PB, Flynn PJ, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol* 2013; 31:4465-70.

Figure Legends

Figure 1. Kaplan-Meier curves for post-recurrence survival for all participants with disease recurrence

The post-recurrence survival of participants with recurrence is shown according to stage of primary tumor (1A), site of primary tumor (1B), and site of recurrent disease (1C). All include the number of patients at risk and p value calculated using the log-rank method.

Figure 2. Kaplan-Meier curves for post-recurrence survival for just those participants who underwent surgical treatment of recurrence with curative intent

The post-recurrence survival of participants with recurrence treated surgically with curative intent is shown according to stage of primary tumor (2A) and site of primary tumor (2B). All include the number of patients at risk and p value calculated using the log-rank method.