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Title

The Effect of a Multidisciplinary Regional Educational Programme on the Quality of Colon Cancer Resection.

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Conflict of interests

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Abstract

Aim

Mesocolic plane surgery with central vascular ligation produces an oncologically superior specimen following colon cancer resection and appears to be related to optimal outcomes. We aimed to assess whether a regional educational programme in optimal mesocolic surgery led to an improvement in the quality of colon cancer specimens.

Method

Following a regional educational programme in the Capital and Zealand areas of Denmark, 686 cases of primary colon cancer resected across six hospitals were assessed by grading the plane of surgery and undertaking tissue morphometry. These were compared to 263 specimens resected prior to the regional educational programme.

Results

Across the region, the mesocolic plane resection rate improved from 58% to 77% ($p<0.001$). One hospital had previously implemented mesocolic plane surgery with central vascular ligation as standard prior to the regional educational programme and continued to produce a high rate of optimal mesocolic plane specimens (68% of all cases). This hospital continued to be more radical when compared to the other five hospitals combined with a greater distance between the tumour and the high tie (median for all cases in fresh specimens: 113 vs. 82 mm), area of mesentery (14,679 vs 9,554 mm^2), and lymph node yield (33 vs. 18). Three of the other hospitals showed

a significant improvement in the plane of surgical resection (46% to 84%, 37% to 92% and 68% to 88%).

Conclusion

A multidisciplinary regional educational programme in optimal mesocolic surgery improved the oncological quality of colon cancer specimens as assessed by mesocolic planes, however, there was no significant effect on the amount of tissue resected centrally. Surgeons who attempt to perform central vascular ligation continue to produce more radical specimens suggesting that such educational programmes are not sufficient alone to increase the amount of tissue resected around the tumour.

What does this paper add to the literature?

Colon cancer surgery is frequently suboptimal with many specimens showing defects into the mesocolon or a failure to resect all of the draining lymph nodes. Multidisciplinary education in optimal mesocolic surgery backed up by rigorous pathological feedback improves the quality of the specimens and should result in better patient outcomes.

INTRODUCTION

Colorectal cancer is common resulting in around 333,000 deaths annually.[1] Optimization of surgery is essential to obtain the best outcomes. Total mesorectal excision (TME) for rectal cancer improves outcomes and surgical educational programmes have reduced the rates of local recurrence and cancer-related mortality.[2–5]

Colon cancer has been relatively neglected and it is important that we determine the optimal surgical techniques. The concept of mesocolic plane surgery with central vascular ligation is associated with the best outcomes reported in the literature to date, with five year cancer-related survival rate of over 89% and reduced local recurrance.[6-8]

West et al. demonstrated that surgeons attempting to perform mesocolic plane surgery with central vascular ligation are more likely to resect the specimen in the mesocolic plane when compared to surgeons using conventional techniques.[9,10] An intact mesocolon has been shown to be associated with 15% greater overall survival at five years compared to cases with significant mesocolic defects, with the difference rising to 27% in stage III disease.[11] West et al., also demonstrated that mesocolic plane surgery with central vascular ligation removes more mesocolon around the tumour and more lymph nodes compared to conventional techniques with around five centimetres of additional tissue at the high tie.[9]

Outcomes for colorectal cancer patients in Denmark were shown to be less favorable than those in other Western European countries.[12] To improve cancer outcomes, the

Danish government implemented a National Cancer Plan in 2000, and in 2001 the Danish Colorectal Cancer Group created the National Colorectal Cancer Database.[13] A small number of individual surgical units showed a spontaneous willingness to engage in quality improvement. For example, in 2008 four surgeons from Hillerød Hospital near Copenhagen were convinced by the evidence and attended a symposium in Erlangen and observed a series of colonic resections using mesocolic plane surgery with central vascular ligation, before implementing a departmental training programme backed up by rigorous and continuous histopathological quality control with direct feedback. Following this process, Hillerød surgeons removed significantly more specimens in the mesocolic plane with a greater distance between the central tie and tumour when compared to other hospitals in the region, which led to improved patient survival.[10,14] Subsequently, a government-funded regional multidisciplinary colon cancer educational programme was held in June 2009, and included detailed education in optimal mesocolic surgery for all surgeons across the region. Following the successful implementation of TME through such educational programmes, it was hoped that Danish colon cancer outcomes would show significant improvement, having remained static until 2008.[15] The aim of the current study was to assess whether the regional educational programme led to oncologically superior resections in the hospitals across the Capital and Zealand regions of Denmark.

METHOD

Patients

Specimen photographs and clinicopathological data were obtained for cases of potentially curable primary colonic adenocarcinoma resected at six hospitals across the Capital and Zealand regions of Denmark. All six hospitals are specialist colorectal centres each providing colorectal cancer surgery for a population of over 250,000 inhabitants. One of the centres, Hillerød Hospital, provided a consecutive series of cases from the start of the pre-education cohort collection, whereas routine photography of all colon cancer specimens was gradually introduced into the histopathology departments of the other hospitals meaning that not all were continuous.

Resections were excluded if they were for pre-invasive adenomas, if the tumour originated in the rectum (defined as fifteen centimetres or less from the anocutaneous junction), if they were operated on as an emergency, or if no clinicopathological data were received.

The pre-education cohort consisted of 263 cases that were operated on prior to the regional educational programme in June 2009. Collection of these cases started in September 2008 and analysis of these data was published in 2010.[10] In total, 93 of these cases were from Hillerød where mesocolic plane surgery with central vascular ligation was performed as standard, and the remainder were from the other five hospitals where conventional low tie surgery was believed to be practiced. Following the regional educational programme, a further 686 cases were collected from the six hospitals until December 2010. Data regarding which individual surgeons had

performed/supervised the operation, the height of the ligation, whether a laparoscopic or open approach was used, and postoperative morbidity/mortality were not available. All resections from Hillerød in both cohorts were either performed or supervised by consultant colorectal surgeons. For the other five hospitals, this was also true for 95.9% of the cases. The remainder were performed by senior colorectal surgical trainees.[14]

Multidisciplinary colon cancer educational programme

The multidisciplinary colon cancer educational programme was held in Helsingor, Denmark over two days in June 2009. Surgeons from each of the six surgical units in the Capital and Zealand regions of Denmark attended along with radiologists, oncologists, and histopathologists. The clinicians who attended were expected to return to their individual units and disseminate the information attained. The programme was lecture based and included sessions on best practice for colon cancer management in the fields of surgery, oncology, imaging, and pathology. These were delivered by a panel of international experts and specifically included detailed instruction on the technical aspects of both open and laparoscopic mesocolic plane surgery with central vascular ligation i.e. the technique previously described by Hohenberger et al.[7] Pathologists were strongly encouraged to provide feedback to their local surgeons on the quality of the mesocolic dissection using a standardised grading system (see below).

Specimen photography and histopathological processing

Histopathologists from the six centres had attended specific education in specimen photography prior to collection of the photographs. Fresh unopened specimens were

digitally photographed in colour by either the surgical team or histopathologists. Standard histopathological procedures were undertaken including a minimum of 48 hours fixation in formalin and serial cross-sectional slicing of the tumour segment at three to four millimetre intervals. Whole fixed specimens were photographed prior to slicing and additional images of the cross-sectional slices were captured. The whole specimens were photographed from the anterior and posterior aspects with the mesentery laid out flat. All photographs included a metric scale for calibration. Histopathological staging was carried out using the International Union Against Cancer TMN version 5.[16] All clinicopathological data were obtained from hospital records and histopathology reports.

Retrospective grading of the mesocolic planes

Grading of the mesocolic planes was carried out retrospectively from the specimen photographs by an independent histopathologist (NPW) who was blinded to the hospital of origin, but not whether the specimens were resected before or after the educational programme. The specimens were graded into three categories: muscularis propria plane (significant defects in the mesocolon that extended down to the muscularis propria), intramesocolic plane (significant defects in the mesocolon not reaching the muscularis propria), and mesocolic plane (intact mesocolon, no significant defects). The grading was based on the worst area, whatever its distance from the tumour.

Tissue morphometry

Tissue morphometry was performed on the whole specimen photographs using ImageScope version 11.2.0.780 (Aperio Technologies Inc., Vista, CA). Both fresh and

fixed specimens were analysed by two independent observers (GSD and ETH) who were blinded to hospital and date of resection. The area of the mesentery, distance between the high vascular tie and the tumour, distance between the high vascular tie and the nearest bowel wall, length of colon, and length of ileum were measured (where applicable). Photographs were not analysed if they were judged to be of poor quality, if the specimen was significantly distorted, or if no metric scale was included in the image. Measurements were not incorporated into the final analysis if either one of the observers deemed the variable unmeasurable. Any specimens where the measurements significantly differed were assessed together with a third observer (NPW) before being re-measured.

Ethical approval

All clinicopathological data and photographs were anonymised and given a unique study number prior to transfer to the United Kingdom. Ethical approval was granted by the Northern and Yorkshire Research Ethics Committee (unique number: 07/MRE03/24). Local ethical approval and individual patient consent was not needed for the study as all data and photographs were collected as part of routine clinical practice.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 22 (IBM SPSS, Armonk, NY). All data was analysed using non-parametric testing with the Mann-Whitney U test and Kruskal-Wallis test as appropriate. Correlation analyses were performed using Spearman’s rho. Analyses

where the p value was less than 0.05 were considered to represent statistical significance.

RESULTS

In total, 686 cases were received following the regional educational programme. Of these, 14 were excluded from subsequent analyses: 11 with missing clinicopathological data and photographs, two emergency resections, and one case where the clinicopathological data did not match the photographs. Therefore 672 cases were analysed in the post-education cohort including 183 from Hillerød Hospital and 489 (range 24 to 135) from the other five hospitals. Clinicopathological data before and after the regional educational programme is shown in table 1 and supplementary table 1. Clinicopathological variables were generally similar between the hospitals.

Plane of Surgery

An assessment of the plane of surgery following the educational programme was able to be made in 133 Hillerød cases and 376 cases (range 24 to 107) from the other hospitals. Across the whole region, the mesocolic plane resection rate significantly improved (58% to 77%, $p < 0.001$). The mesocolic plane rate was maintained in Hillerød specimens (75% before vs. 68% after, $p = 0.256$) and was significantly improved in the other hospitals combined (48% before vs. 80% after, $p < 0.001$). When analysed individually, three of the other hospitals showed an improvement in the mesocolic plane rate (47% to 84%, $p < 0.001$; 37% to 93%, $p < 0.001$; 68% to 88%, $p = 0.026$). There was no significant change in two of the other hospitals (50% to 51%, $p = 0.892$; 100% to 83%, $p = 0.745$). The plane of surgery data for all six hospitals when stratified by site of tumour is shown in figure 1.

Tissue Morphometry

Following exclusions, 155 fresh and 101 fixed post-education specimens from Hillerød, and 157 fresh and 378 fixed specimens from the other five hospitals were suitable for morphometric analysis. There was good correlation between the two independent observers for both fresh and fixed specimens with the area of mesentery (R = 0.910 fresh, R = 0.871 fixed), tumour to high tie (R = 0.884 fresh, R = 0.864 fixed), nearest bowel wall to high tie (R = 0.872 fresh, R = 0.880 fixed), length of colon (R = 0.973 fresh, R = 0.936 fixed), and length of ileum (R = 0.969 fresh, R = 0.901 fixed).

The tissue morphometry data for fresh and fixed specimens are shown in table 2. There was a significant increase in the amount of tissue resected between the tumour and the high vascular tie in the left sided cases from Hillerød and the other five hospitals following the educational programme, leading to an increase in the area of mesentery resected. Right sided and transverse tumours did not consistently change. Cases resected in Hillerød continued to be more radical following the educational programme.

When the other hospitals were analysed individually, there were no consistent differences in tissue morphometry characteristics before and after the educational programme (supplementary tables 1–5). There was a smaller distance between the tumour and high vascular tie and smaller area of mesentery resected in the post-educational cases in all of the other hospitals when compared to Hillerød (figure 2).

DISCUSSION AND CONCLUSIONS

The effect of a multidisciplinary regional educational programme in optimal mesocolic surgery is unknown and has been assessed in the current study across the Capital and Zealand regions of Denmark. Surgeons at Hillerød Hospital spontaneously implemented mesocolic plane surgery with central vascular ligation as standard for all cases of operable colon cancer prior to the regional educational programme. This occurred following attending a symposium in Erlangen and implementing a departmental training programme backed up by rigorous and continuous histopathological quality control. They maintained the high rate of mesocolic plane resections and central radicality demonstrated before the programme, although interestingly the proportion of mesocolic plane resections fell for left sided resections. This may reflect the higher number of difficult to resect pT4 tumours in the post-education cohort. Importantly the number of muscularis propria specimens did not increase. The radicality of left sided resections increased with a greater distance between the tumour and high tie and area of mesentery resected. This was associated with an overall increase in lymph node yield, but not the number of involved nodes. There were no significant changes to right sided and transverse specimens. Hillerød continued to produce the most radical specimens across the region, and the tumour to high tie measurements are comparable to resections undertaken in centres reporting the best outcomes in the literature including Erlangen (right sided 118 mm, left sided 126 mm), Tokyo (right sided 100 mm, left sided 122 mm), and St. Marks (right sided 107 mm, left sided 122 mm).[17,18] Whilst data on mortality and recurrence were not available for the current study, Hillerød have recently published their longer term outcome data following the switch to mesocolic plane surgery with central

vascular ligation and report a 10% greater four year disease-free survival on a population basis compared to other centres in the region.[14]

When looking at the other five hospitals combined, the mesocolic plane resection rate significantly improved, and was driven by significant improvements in three hospitals. A fourth hospital continued to produce a high rate of mesocolic plane excisions whereas the fifth made no significant improvement with only around 50% mesocolic plane specimens. This suggests that multidisciplinary regional education in optimal mesocolic surgery had a direct effect on the quality of colon cancer specimens in most centres and should lead to a greater improvement in absolute survival for colon cancer in Denmark in addition to that reported in recent years, which is thought to be primarily due to a reduction in one year mortality and greater use of chemotherapy in stage III disease.[19] Previous studies have shown that mesocolic plane surgery is associated with a 15% improvement in overall survival compared to cases with major defects, rising to 27% in stage III disease.[11] The reasons for the failure of one hospital to improve are worthy of further investigation and might reflect differences in case mix or a failure to convince the surgical team of the importance of mesocolic plane excision.

Whilst mesocolic planes improved or were maintained in most centres, there was very little change in the radicality of the specimens as assessed using tissue morphometry. It was therefore unsurprising that the lymph node yield in the other hospitals combined did not change. This suggests that whilst the regional educational course was successful in convincing delegates of the importance of mesocolic planes, they were not convinced of the importance of central vascular ligation in the same way that surgeons from Hillerød were or further experience may be required before a change

is noted. The potential benefits of high tie surgery have been debated for decades with a number of studies showing a benefit whilst others show no difference. Centres undertaking mesocolic plane surgery with central vascular ligation report the best outcomes in the literature, however, they are confounded by reporting higher mesocolic plane resection rates so the true additional benefit of a high tie is hard to dissect from the unquestionable benefit of mesocolic plane surgery. Some have called for a randomised trial of high versus low tie surgery in the context of excellent mesocolic surgery confirmed by rigorous pathological quality control, something that was missing from earlier studies.[20] There continues to be concern that central vascular ligation may be associated with increased morbidity, with some studies reporting more genitourinary complications in left-sided resections compared to conventional low ties.[21] However, this study included resection of the para-aortic lymph nodes which are generally not resected with central vascular ligation. In the Copenhagen region, central vascular ligation has been shown to be associated with a significant increase in intraoperative organ injuries and severe non-surgical complications.[22] The learning curve for central vascular ligation is as yet not fully understood, although Hillerød have shown that it can be successfully adopted without an increase in complications.[23]

There were several limitations to our study. Firstly we were limited by small case numbers from some of the hospitals, particularly when breaking the results down according to the site of the tumour. We were also limited by missing photographs with only fresh or fixed pictures being available in the majority of cases. The quality of some of the photographs was poor with missing metric scales, photographs not being taken from directly above, no marker for the position of the tumour and high tie etc. This not only reduced the number of measurements that we could attain for each individual

hospital but may also have introduced a degree of bias. Finally, as the study was non-randomised, it is possible that differences in case mix between the hospitals and over time affected the specimen quality and measurements.

We have shown that a regional multidisciplinary educational programme focusing on the importance of high quality colon cancer surgery has led to a marked improvement in the mesocolic plane resection rate. Only one individual centre continued to produce a low rate of mesocolic plane specimens. Despite the improvement in mesocolic planes, there was no significant improvement in the central radicality of the specimens suggesting that the evidence to convince surgeons to undertake central vascular ligation remains immature. With a significant survival benefit expected from improving the planes of surgery, regional and national educational courses are likely to be an effective way of improving colon cancer outcomes and bringing them back in line with the improvements that have been reported for mesorectal surgery in rectal cancer over recent years.

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FIGURE LEGENDS

Figure 1: Plane of surgery data for each hospital before and after the regional educational programme in right sided (A), transverse (B), and left sided (C) resections.

Figure 2: Tissue morphometry data for each hospital after the regional educational programme according to the site of the tumour in terms of area of mesentery (A), distance from the high vascular tie to the tumour (B), distance from the high vascular tie to the nearest bowel wall (C), and length of colon resected (D).

TABLE LEGENDS

Table 1: Clinicopathological variables for Hillerød hospital and the other hospitals combined both before and after the regional educational programme. Transverse tumours include those located in the flexures. Values in parentheses represent valid percentages rounded to the nearest whole number. n = number of cases.

Table 2: Fresh and fixed specimen tissue morphometry data for Hillerød hospital and the other hospitals combined both before and after the regional educational programme according to the site of the tumour. Transverse tumours include those located in the flexures. AoM = area of mesentery (mm^2), THT = distance from the high vascular tie to the tumour (mm), NBHT = distance from the high vascular tie to the nearest bowel wall (mm), LC = length of colon resected (mm), LI = length of ileum resected (mm), N = number of cases, IQR = interquartile range, Hill = Hillerød, Oth = other five hospitals, B = before educational programme, A = after educational programme

Supplementary Table 1: Clinicopathological variables according to individual hospital before and after the regional educational programme. Transverse tumours include those located in the flexures. Values in parentheses represent valid percentages rounded to the nearest whole number. n = number of cases.

Supplementary Table 2: Fresh and fixed specimen tissue morphometry data for ‘other hospital 1’ before and after the regional educational programme according to the site of the tumour. Transverse tumours include those located in the flexures. AoM = area of mesentery (mm2), THT = distance from the high vascular tie to the tumour (mm),

NBHT = distance from the high vascular tie to the nearest bowel wall (mm), LC = length of colon resected (mm), LI = length of ileum resected (mm), N = number of cases, IQR = interquartile range.

Supplementary Table 3: Fresh and fixed specimen tissue morphometry data for ‘other hospital 2’ before and after the regional educational programme according to the site of the tumour. Transverse tumours include those located in the flexures. AoM = area of mesentery (mm2), THT = distance from the high vascular tie to the tumour (mm), NBHT = distance from the high vascular tie to the nearest bowel wall (mm), LC = length of colon resected (mm), LI = length of ileum resected (mm), N = number of cases, IQR = interquartile range.

Supplementary Table 4: Fresh and fixed specimen tissue morphometry data for ‘other hospital 3’ before and after the regional educational programme according to the site of the tumour. Transverse tumours include those located in the flexures. AoM = area of mesentery (mm2), THT = distance from the high vascular tie to the tumour (mm), NBHT = distance from the high vascular tie to the nearest bowel wall (mm), LC = length of colon resected (mm), LI = length of ileum resected (mm), N = number of cases, IQR = interquartile range.

Supplementary Table 5: Fresh and fixed specimen tissue morphometry data for ‘other hospital 4’ before and after the regional educational programme according to the site of the tumour. Transverse tumours include those located in the flexures. AoM = area of mesentery (mm2), THT = distance from the high vascular tie to the tumour (mm), NBHT = distance from the high vascular tie to the nearest bowel wall (mm), LC = length

of colon resected (mm), LI = length of ileum resected (mm), N = number of cases, IQR = interquartile range.

Supplementary Table 6: Fresh and fixed specimen tissue morphometry data for ‘other hospital 5’ before and after the regional educational programme according to the site of the tumour. Transverse tumours include those located in the flexures. AoM = area of mesentery (mm2), THT = distance from the high vascular tie to the tumour (mm), NBHT = distance from the high vascular tie to the nearest bowel wall (mm), LC = length of colon resected (mm), LI = length of ileum resected (mm), N = number of cases, IQR = interquartile range.