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GOOD SURVIVAL OUTCOMES IN PATIENTS WHO UNDERGO BOWEL RESECTION AFTER STENT FAILURE IN MALIGNANT BOWEL OBSTRUCTION

Salman E Ahmed	MRCS, Department of General Surgery, James Cook University Hospital, Marton Road, Middlesbrough, United Kingdom, TS4 3BW
Ali Ghareeb*	MB Bchir, Department of General Surgery, James Cook University Hospital, Marton Road, Middlesbrough, United Kingdom, TS4 3BW* Corresponding Author
Nick Wadd	FRCR, Cancer Services, James Cook University Hospital, Marton Road, Middlesbrough, United Kingdom, TS4 3BW
Madan Jha	FRCS, Department of General Surgery, James Cook University Hospital, Marton Road, Middlesbrough, United Kingdom, TS4 3BW

ABSTRACT

Background Colonic stents are inserted to relieve malignant obstruction. The longer the colonic stent remains in situ the greater the risks of complication. In this study, we aim to investigate the overall outcomes in patients with unresectable colorectal metastatic cancer being treated with colonic stents with or without palliative chemotherapy.

Methods This retrospective study was conducted in a tertiary oncology centre. All patients with an obstructing large bowel malignancy who had colonic stents inserted between August 2005 and April 2015 were included and followed up until death. The primary outcome measure was median survival.

Results Stenting was attempted in 84 patients with large bowel obstruction, 72 (85.7%) of which were successful. Sixty-four (76.2%) of the attempted stents were palliative. Of these, twenty-eight patients with inoperable disease were stented and later received palliative chemotherapy, while thirty-six patients were found to have poor performance status and were unsuitable for any form of chemotherapy. Median survival for these groups was 235 days (95% CI: 165-330 days) and 121 days (63-328 days), respectively. Five patients in the chemotherapy group underwent bowel resection. Median survival was found to be significantly higher at 560 days as compared to all other patients who received chemotherapy (n=24), for whom median survival was 210 days (p=0.002).

Conclusions The survival of patients who receive bowel resection after stent failure is higher than that of patients who retain the stent. For patients with suitable physical status, expected to survive more than 12 months and presenting with colonic obstruction, colostomy or surgical resection of the primary may be a suitable alternative to stent and this should be investigated in future prospective trials.

KEYWORDS :

Introduction

Between April 2014 and March 2015, 30122 patients were diagnosed with bowel cancer in England and Wales. Despite early cancer detection as a result of screening programme, the rate of diagnosis following emergency admission has remained steady (20.8% in 2011-12 vs. 20.5% in 2015-16).[1] The 90 day post-operative mortality in emergency or urgent operations has remained high when compared with scheduled procedures 11.9% vs. 1.8% (2015-16).[1] Since the introduction of self-expanding metallic colonic stents (SEMS) in the 1990s, there has been a trend to offer colonic stents in patients with obstructing cancers in order to avoid emergency operations and the need for stoma. SEMS may also provide a bridge to surgery by allowing decompression of the bowel and also can be used definitively in palliative treatment. NICE guidance (CG131) and UK multidisciplinary peer review suggest self-expanding metallic stents should be considered for all patients with acute large bowel obstruction with incurable disease or in patients unsuitable for surgery.[2,3]

Few studies review the long term efficacy of colonic stents and even fewer investigate patients' quality of life following insertion of a colonic stent.[4] Furthermore, there is a lack of studies assessing the potential risks and complications of colonic stent in patients receiving palliative chemotherapy, and the possible effects of the stent on delivery of the chemotherapy agent to the active site. There is evidence of an increased risk of bowel perforation in stented patients on Bevacizumab.[6,7,8] The longer the stent remains *in situ*, the greater the risk of complications.[1]

In this study, we primarily investigated the survival of patients with colonic stents deployed to relieve malignant obstruction, with or without palliative chemotherapy.

Methods

Study Design

This is a retrospective, single-centre study conducted in a bowel cancer tertiary referral centre serving approximately 1.5 million people in the North East of England.

Study Participants

All patients who presented with large bowel obstruction and subsequently underwent colonic stent placement between August 2005 and April 2015 are included in this study. All patients were imaged with CT-scan and assigned a Duke's stage in a colorectal MDT where further management was discussed. Patients whose metastases were deemed operable and those in whom stenting was used as bridge to surgery were excluded from final analysis. Inoperable metastatic disease was defined as metastatic disease involving one or more organs which is not amenable to surgical resection as decided in the colorectal MDT. Patients with oligometastases were referred to other surgical MDTs and also excluded from analysis. Patients deemed suitable for further treatment were seen by the oncologist to discuss initiation of chemotherapy. The final decision to commence chemotherapy was then made by the oncologist. Performance status was assessed by colorectal specialist nurses and the consultant colorectal surgeon and measured by the American Society of Anaesthesiologists physical status classification system. Stent placement was considered a failure if whilst receiving chemotherapy patients became obstructed or perforated. Stent movement during the chemotherapy cycle was considered a good response to treatment.

Data Collection

A prospectively-collected database of all the colonic stent patients is maintained in a radiology department electronic record system. Stent placement was carried out as a joint procedure between an accredited colonoscopist and an interventional radiologist. Prospectively-collected information on cancer histological type, disease stage, success or failure of stent placement and complications is kept in an electronic record system collected by the colorectal multidisciplinary team. Patients who underwent colonic stent placement were admitted for overnight observation and an abdominal x-ray was performed 24 hours post-operation. Information on chemotherapy regimens, complications and follow up was retrieved from oncology department electronic record system.

Data analysis

Data was analysed using BioStat 2016 (AnalystSoft). Overall survival

was estimated using the Kaplan-Meier method. Only death was considered an event in the survival analysis, which was calculated from the date of stent placement. Log-rank survival analysis was performed for comparison and a cut-off of $p<0.05$ was considered to be significant. Cox regression was performed for the multivariate analysis.

Results

Sub-group breakdown

Stent insertion was attempted in a total of 84 patients with large bowel obstruction due to colorectal cancer (Figure 1). Seventy-two procedures (85.7%) were successful. Among the 12 patients who failed the attempted stent, only 4 based on their physiological reserve were subsequently operated with median survival of 122 days (17-1110 days - 95% CI). The remainder were too unfit for any intervention and were managed with best supportive care with a median survival of 12 days (7 – 49 days). Eight patients were stented as bridge to surgery with curative intent and were excluded from further analysis.

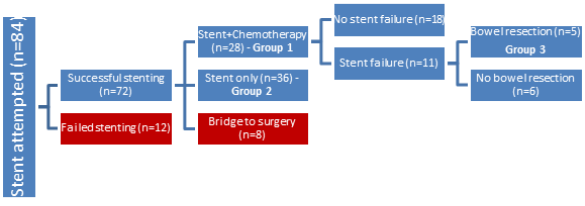


Figure 1: Breakdown of study population

A group of 28 patients (33.3%) with inoperable metastatic disease were stented to relieve the obstruction and subsequently received palliative chemotherapy (Stent and chemotherapy group, FIG 1). A group of 36 patients (42.9%) was found to have poor performance status and was therefore unsuitable for any form of chemotherapy (Stent only group, FIG 1). In this group, stenting was deployed as definitive palliation. Table 1 shows the general characteristics of the stent only group and the stent and chemotherapy group from which further subgroups are derived (FIG 1). The patients who received stent only are not of further interest to this study and so only their median survival is analysed further.

	Stent only	Stent and chemotherapy
n	n=36	n=28
Median age	80.5	65
Male : Female	5 : 4	5 : 4.3
Stage II Disease	5.5% (n=2)	0%
Stage III Disease	27.8% (n=10)	0%
Stage IV disease	66.7%(n=24)	100% (n=28)

Table 1: Demographics and disease stage for patients in the stent only and stent and chemotherapy groups

In the stent and chemotherapy group, pre-chemotherapy baseline prognostic test showed a raised white cell count in 44%, raised platelets count in 48%, low albumin in 16% and a raised alkaline phosphatase in 32%. Most patients received an Oxaliplatin-based chemotherapy first line. The choice of second line chemotherapy was most often Irinotecan-based, either as single agent or as combination chemotherapy in the FOLFIRI regimen. Twelve patients were suitable to receive second-line chemotherapy, and among them 4 patients also received Bevacizumab.

A variety of complications were seen in the stent and chemotherapy group (Table 2). Median time to stent failure for group 1 was 180 days. Out of 4 patients who received Bevacizumab, 3 perforations were recorded.

Post chemotherapy side effects	
Diarrhoea	28% (n=8)
Stent migration (good response)	14%(n=4)
Obstruction (Stent failure)	21% (n=6)
Perforation (Stent failure)	14% (n=4)
Sepsis	3.5% (n=1)
Subsequently operated	17.8% (n=5)
Median stent longevity	180 days (102-222 days 95% CI)
Median post-stenting survival	235 days (165-330 days 95% CI)

Table 2: frequency of stent related side effects, good outcomes and overall survival in the group who received both stent and chemotherapy

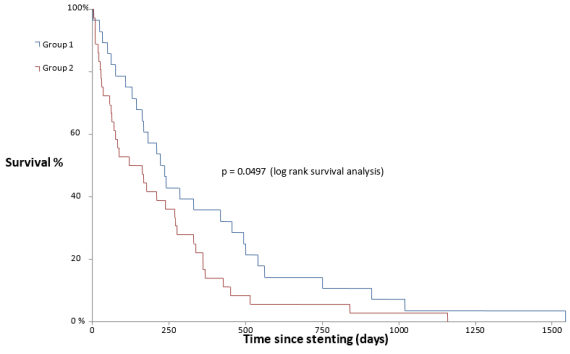
Survival of patients who received stent for malignant large bowel obstruction Overall, median patient survival after stent was 228 days (n=64). The median survival for the stent and chemotherapy group was 235 days (95% CI: 165-330 days), while that of the stent only group was 121 days (63-328 days) which was significantly less (p=0.0497)).

Analysis of the group which received stent and chemotherapy revealed a median survival for patients who received first-line chemotherapy of 162 days (108-284 days), while for patients who received second-line chemotherapy median survival was 241 days (222-418 days 95%CI). Log rank analysis of Kaplan-Meier survival for first and second-line chemotherapy showed no significant difference between the two groups (p=0.824; figure 2). Overall, chemotherapy following stenting was associated with increased survival (p=0.0084; Hazard Ratio=0.43).

Whilst on chemotherapy, stents fell out in 4 patients, which is a marker of good response to treatment. This small subgroup showed a median survival of 493 days (455-750 days), while the remainder of group 1 (n=24) had a median survival of 210 days (130-241), which is significantly less (p=0.0254).

Survival of patients who received resection after delayed stent failure

We also analysed the effect of operative intervention after delayed stent failure in the group receiving chemotherapy (n=28; Figure 1). Five patients in this group (17.8%; table 2) went on to have palliative resections because of delayed stent failure. Importantly, the median survival in this subgroup was shown to be 560 days (39-1080 days 95% CI) significantly longer when compared to the remainder of this group (n=23) whose median survival was 210 days (120 – 299; p=0.002; Figure 3).



Time since stenting (days)

Figure 2: Kaplan-Meier Survival curve of overall survival in groups 1 and 2

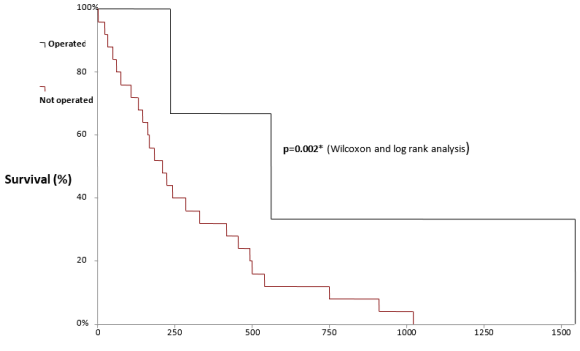


Figure 3: Kaplan-Meier Survival Curves for Group 1 (chemo and stent) operated vs. non-operated

Discussion

Since 1993, colonic stents have been used as an alternative to

defunctioning colostomy or surgical resection of the tumour to palliate left sided large bowel obstruction.[9] In patients with malignant large bowel obstruction and potentially curable disease, stent was found to be useful in minimizing stoma rates at subsequent surgery (CReST 3).[10] However, there are few studies of inoperable patients treated with stent alone or which compare a stent to colostomy or resection. These studies emphasized the success of the procedure and discussed important short-term complications. In studies which investigated the primarily the benefits of the stent versus stoma in terms of quality of life, hospital stay and readmission rates, survival analysis was lacking.[11]

Survival for patients with metastatic colorectal cancer has improved significantly over the last 20 years. This can be attributed to advances in diagnostic and staging techniques. [1] Using these advances, multidisciplinary treatment can be offered to the patients with curative intent. These may include multiple segment liver metastasectomy, resection of lung metastasis and single beam radiotherapy (SBRT). The evolution of new chemotherapeutic agents such as Irinotecan and Oxaliplatin in addition to biochemical modulation of 5 Fluorouracil has also contributed to the improved outcome.[12,13] Tumour DNA is analysed to assess RAS mutations in order to determine suitability for certain chemotherapy agents. As a result, survival for patients with inoperable disease treated with chemotherapy alone has increased to a median of 27.8 months (FIRE 3).[5] Our study primarily focused on obstructed patients treated with stent insertion and palliative chemotherapy, shows a much shorter survival (median 235 days).

In current chemotherapy trials most patients now receive two lines of chemotherapy containing at least four active agents (5 Fluorouracil or Capecitabine, Irinotecan, Oxaliplatin, Cetuximab, Bevacizumab, Alfibercept and Regorafenib).[14,15,16,19,20,24] A national report on systemic anti-cancer therapy (SACT) between Jan 2014 and Dec 2014 shows the most commonly prescribed regimens in England were FOLFOX, FOLFIRI and XELOX.[21] A significant proportion of patients received Bevacizumab or Cetuximab in addition to standard chemotherapy regime, while a further cohort received third line single agent Cetuximab. Some general and drug-specific side effects such as GI and cardiac toxicity, neutropenic sepsis and increased thrombogenecity were observed with chemotherapy agents and therefore a tailored and individualised approach is recommened by SACT.[24, 25] Agents such as VEGF receptor inhibitors (Bevacizumab and Aflibercept) may increase the risk of bleeding or perforation.[6,7]

There are no randomised studies comparing resection of the primary tumour versus no resection in patients receiving palliative chemotherapy. Faron et al [17] suggests patients with resected primary in the presence of unresectable metastasis survive longer than those with a primary tumour *in situ*. It has been a common practice in the UK to offer chemotherapy and not to consider resection of the primary unless clinically indicated. This strategy however remains debatable in the light of current advances in chemotherapy.[18] Meta-analysis of treatment strategy in malignant large bowel obstruction shows stents do not seem to offer a better outcome than surgery, and there are more late onset complications with stents.[26] Xianipoulus et al [23] randomised 30 patients between colostomy and stent. Survival was similar between both groups, with a shorter hospital stay for stented patients. Fiori et al [22] recruited 22 patients with chronic sub acute obstruction and there was no difference observed between stent and stoma group survival.

The lower than expected survival in our study of 235 days (7.8 months) versus 27.8 months in the FIRE 3 trial [5] is an important result. Assuming that both studies had groups of similar performance status, stenting is associated with poor survival. This does not necessarily mean that the presence of a stent compromises the delivery of chemotherapy agent to the target tissue, but this should be investigated in future studies. Given that resection of the primary in unresectable metastatic disease offers favourable survival, the balance of surgical risk, complications and quality of life in resection and stenting should be discussed with patients.

It is important to highlight that our study does not include asymptomatic patients who received palliative chemotherapy. It is shown that, there was no significant survival difference in the patients receiving 1st-line versus 2nd-line chemotherapy (Graph 3). The lack of ability to offer Bevacizumab in stented patient due to its increased risk of perforation may be a contributory factor to overall lower survival in group 1. An overall low survival in group 1 as compared to the FIRE3 study, and no survival difference between patients who received 1st-line and those who received both 1st and 2nd-line chemotherapy (Figure 2) raises the question of whether the presence of a stent is associated with worse survival, as perhaps chemotherapy is less effectively delivered in the presence of a stent. However, it is difficult to draw an inference based on our results. Furthermore, there is a relative lack of evidence in literature describing long term survival in patients with malignant obstruction treated with stent and chemotherapy.

Our study cohort comprised 72 patients successfully stented for malignant large bowel obstruction of whom 28 received chemotherapy (Figure 1). In group 1, the median stent longevity was 180 days and median post-stenting survival was 235 days (table 2). Falling out of stent during chemotherapy was considered a marker of good response to the treatment with demonstrable survival benefit. Furthermore, it was observed that patients who underwent resection due to stent failure whilst on chemotherapy have a significant survival benefit (Figure 3). Two randomised trials looking into the outcomes of colonic stents were too small to make any firm recommendations.[22,23]

We studied the complications of patients stented to relieve malignant large bowel obstruction, managed with or without chemotherapy. All patients were followed up until death. As a retrospective, single-centre study our results have certain limitations, such as the small size of the group who received resection of the primary (n=5). This however reflects the fact that this practice is not first-line management. These limitations should be addressed by future randomised control trials.

Conclusions

The survival of patients with a stented colorectal cancer and metastatic disease is low, whether or not they are treated with chemotherapy. Due to the presence of stent patients may not receive optimal first line chemotherapy. Second line chemotherapy is less frequently given due to the increased risk of perforation. Many patients experience stent complications. If chemotherapy is planned the managing team should discuss the best method of palliation with the patient. For patients whose performance status suggests they may live longer than 12 months, we believe that colostomy or surgical resection of the primary could be a better option. This would avoid stent complications and potential barriers to effective delivery of chemotherapy and would allow the option to use all available chemotherapy drugs with potential benefit on long term survival. Further multi centre prospective studies are needed to elaborate the potential effect of chemotherapy on overall survival and patient outcome in patients with stent *in situ*.

Conflicts of interest

None.

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Acknowledgments

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