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Patterns of surveillance for colorectal cancer: Experience from a single large tertiary institution

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Full title: Patterns of surveillance for colorectal cancer – Experience from a single large tertiary institution.

Short title: Surveillance for colorectal cancer

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ABSTRACT

Aim:

Colorectal cancer surveillance is an essential part of care and should include clinical review and follow-up investigations. There is limited information regarding post-operative surveillance and survivorship care in the

Australian context. This study investigated patterns of colorectal cancer surveillance at a large tertiary institution.

Methods:

A retrospective review of hospital records was conducted for all patients treated with curative surgery between January 2012 and June 2017. Provision of clinical surveillance, colonoscopy, computed tomography (CT) and carcinoembryonic antigen (CEA) within 24 months post-operatively were recorded. Kaplan-Meier estimates were used to evaluate time-to-surveillance review and associated investigations.

Results:

A total of 675 patients were included in the study. Median time to first post-operative clinical review was 20 days (95% confidence interval (CI) 18-21) with only 31% of patients having their first post-operative clinic review within two weeks. Median time to first CEA was 100 days (95% CI 92-109), with 47% of patients having their CEA checked within the first three months, increasing to 68% at six months. Median time to first follow-up CT scan was 262 days (95% CI 242-278) and for colonoscopy, 560 days (95% CI 477-625). Poor uptake of surveillance testing was more prevalent in patients from older age groups, those with multiple co-morbidities, and higher stage cancers.

Conclusion:

Colorectal cancer surveillance is multi-disciplinary and involves several parallel processes, many of which lead to inconsistent follow-up. Further prospective work is required to identify the reasons for variation in care and which aspects are most important to cancer patients.

Keywords: colorectal neoplasms, surveillance, survivorship

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer in Australia and the second most common cause of cancer related death (1). Despite advances in surgical techniques and oncological therapies, survivors are still at risk of developing locoregional recurrence, distant metastasis, or metachronous colon cancers (2). Of these recurrences, 80% will occur within the first two and a half years of treatment, and 95%, within five years (3). As such, surveillance forms an important aspect of survivorship care and aims to identify recurrent or new disease early enough to institute treatment with curative intent. Unfortunately, adherence to surveillance guidelines can be variable. Patterns of surveillance have been investigated internationally, however there has been significantly limited published data regarding the provision of post-operative surveillance for colorectal cancer in the Australian setting (4, 5).

METHODS

All patients who underwent curative surgery for colorectal cancer at Western Health (Melbourne, Australia) between January 2012 and June 2017 inclusive were identified using a prospectively maintained database, and their institutional medical records were reviewed. Patients were excluded from the study if their follow-up care had been transferred to another institution or provider, or if they did not receive at least one post-operative review, noting that all patients were eligible to receive at least three independent follow-up interactions during the study period before being discharged from clinic.

Information collected included clinical and sociodemographic characteristics and date of death (if applicable). The American Society of Anesthesiologists (ASA) score was obtained for all patients. This is a widely used five category scale which is simple to measure and can help characterise a patient's overall level of fitness for surgery, with a score of one given to a completely healthy patient, and a score of five reflecting a moribund patient (6). Tumor characteristics were collected, with the Australian clinicopathological staging score (ACPS) recorded for all patients. The ACPS system is the recommended method of staging in Australia as it utilizes clinical, radiological, operative and pathological information before a stage is allotted (7). This is in contrast to Dukes' system, which is based solely on the pathologic examination of the resected carcinoma. It allows classifications of all cases of colorectal cancer seen, whether treated by resection, palliative surgery, local excision or not at all (8). A SEIFA score was also recorded for every patient based on their primary place of residence. This score is an index of relative socio-economic disadvantage and is measured out of five. A score of 1 suggests more disadvantage, while a score of 5 reflects less disadvantage (9).

Receipt of surveillance hospital clinical review, colonoscopy, Computed Tomography of the chest, abdomen and pelvis (CT CAP) and carcinoembryonic antigen (CEA) for the first two years after surgical resection was recorded. Uptake of surveillance testing was compared to our institution's post-operative review and

surveillance protocol which remained unchanged during the study period and was agreed upon by health providers before the study began. This protocol complied with the American Cancer Society and the National Comprehensive Cancer Network (NCCN) protocol; with the only exception being CT scans which were performed annually for the first two years only (10, 11). Our protocol consisted of a two-week post discharge clinic appointment, followed by a three-monthly clinical review (including CEA measurement) for the first two years, a colonoscopy at 12 months after surgery (unless colonic investigations were not complete prior to surgery) and CT scans at 12 and 24 months after surgery. Requests for CEA were completed on blood slips, to be performed by one of Victoria's leading pathology providers directly linked to our hospital network. This ensured that all results were easily accessible to our clinicians and that patients had easy access to local services. CT scans and colonoscopies were also requested to be done at one of the three sites within our own institution. These sites are distributed across the West of Melbourne and covers the majority of the catchment of our patients. We acknowledge that access to these two tests can be a barrier but during our face to face clinic appointments, we aimed to facilitate a suitable arrangement for those who voiced their challenges.
All reviews were conducted in the same public colorectal clinic, with reviews conducted by medical staff of varying degrees of seniority (i.e. junior medical staff through to consultants) following our standardised care plan. All patients who were non-English speaking were provided with an interpreter during their clinical appointment.

Statistics

Time between discharge and each surveillance test were analysed for the 24-month post-operative period using the Kaplan-Meier estimator. Patients were censored at death or at the end of follow-up, whichever occurred first. Median time to event and 95% confidence intervals (CI) were obtained directly from the Kaplan-Meier estimates. The Log-rank test was used to assess potential effects of baseline clinical and sociodemographic patient characteristics. Significance was defined as a p-value of less than 0.05 (no adjustment for multiple testing) and all p-values correspond to two-sided tests. All statistical analyses were performed using R (12).

Ethical considerations

Institutional human research ethics committee approval was obtained (approval number QA2018.11).

RESULTS:

Between January 2012 and June 2017, 755 patients with colorectal cancer were treated surgically. Sixty-six were excluded from the study due to incomplete data. Thirteen patients underwent palliative procedures only, and one had anal cancer, and were also excluded. The remaining 675 public patients were included in the analysis. Patient characteristics and tumor staging information are shown in Table 1 (7, 13). At the conclusion of data collection, 172 patients were deceased (25%).

Provision of colorectal cancer surveillance

Median time to first post-operative clinical review was 20 days (95% CI 18-21) with only 31% of patients having their first post-operative clinic review within two weeks. Median time to second clinical review was 42 days (95% CI 35-42). At three months, 83% of patients had received their first clinical review, while at six months this figure increased to 89%. Median time to first CEA was 100 days (95% CI 92-109), with 47% of patients having their CEA checked within the first three months, increasing to 68% at six months. Median time to second CEA was 92 days (95% CI 91-98). Median time to first follow-up CT scan was 262 days (95% CI 242-278). (Fig. 1). Median time to first colonoscopy was 560 days (95% CI 477-625) with only 25.9% having a colonoscopy performed within the first year, increasing to 49.5% within 18-months. (Fig. 2).

Factors associated with receipt of colorectal cancer surveillance

Older age was associated with a reduced number of patients adhering to our recommended surveillance guidelines for first and second CEA ($p < 0.001$), CT CAP ($p < 0.001$) and colonoscopy ($p = 0.02$). First clinical review with regards to age influences was similar ($p = 0.13$), but there was a significant reduction in patients having the correct timing of their second clinical review ($p < 0.001$). Higher ASA scores also affected the first and second CEA ($p = 0.01$ and $p < 0.001$ respectively) as well as first CT CAP and colonoscopy ($p < 0.001$ respectively). This was also observed in individuals with a higher ACPS, with respect to time for first and second CEA, CT CAP and colonoscopy ($p < 0.001$). Other factors such as English proficiency, sex and lower SEIFA scores had no association with adherence to our surveillance programme. Finally, living further away

from hospital affected the uptake of surveillance testing with respect to first and second CEA testing ($p = 0.01$ and $p < 0.001$ respectively) and second clinic visit ($p = 0.02$) only.

DISCUSSION:

Controversy still exists with regards to optimal timing, frequency and duration of follow-up for colorectal cancer survivors, with international organisations yet to establish a uniform consensus. Multiple surveillance strategies have been proposed by such organisations, with several studies conducted to explore the merit of intensive surveillance programs in the post-operative period. Several systematic reviews and meta-analyses report a modest but significant overall survival benefit for intensive surveillance (4, 14-17). However, these meta-analyses are limited by the heterogeneity of the population studied and the wide variation in surveillance programs implemented. Furthermore, many studies include patients with stage I disease, whose outcomes are highly favourable post resection compared to those with more advanced malignancy. More recently, a meta-analysis conducted by Mokhles et al, which included data from seven randomised controlled trials, showed no survival benefit for patients receiving more intensive surveillance (18). This finding is in line with more recent studies such as the COLOFOL trial, a prospective randomized multicentre trial which compared two follow-up regimes in over 2500 patients from 24 institutions (19). It is also in line with analysis of data from the National Cancer Database, where no significant difference in time to detection of recurrence or overall survival was found with intensive surveillance (20). Despite these more recent studies, current Australian guidelines recommend that those who undergo resection for colorectal cancer with curative intent, and who are fit for further intervention, receive intensive follow-up (21). Our institution aims to follow guidelines endorsed by the American Cancer Society and NCCN, with the only exception being with respect to CT CAP, which is performed annually for the first two years only; a protocol that has been agreed by our local multidisciplinary team and has been in place over our study period (10, 11).

To our knowledge, our study is the first retrospective cohort study in Australia to explore uptake of guideline recommended surveillance in patients treated for colorectal cancer. It provides the largest "real world" data on colorectal cancer follow up within a government run single institution within the Asia–Pacific region. It reflects the multicultural population that our hospital serves, with a large proportion of patients from lower socioeconomic backgrounds. Our study highlights strong adherence to provision of clinical review as per our institutional guidelines. However, figures suggest that our institution is not adequately following CEA guideline recommendations. Our study also showed that the uptake of surveillance CT CAP was earlier than recommended. This may be partially affected by those with more advanced disease who were potentially participating in oncological trials which necessitated more frequent imaging. It must be noted that during data acquisition, we included only CT scans completed for surveillance purposes only. This eliminated the inclusion of CT scans preformed for alternate reasons to surveillance, or for non-related conditions, which could have affected our results. Our study also highlighted a significant delay in the provision of recommended colonoscopy surveillance. This is significantly less than two out of three previous Australian studies (22-24). Despite the lack of compliance with surveillance in our cohort, it does not seem to negatively impact patient survival. Our survival rate of 75% determined at the conclusion of our study, compares favourably with other studies which quote an overall five year survival ranging between 70-81.9% (25-28). This is consistent with the literature for the most part and calls into question the value of intensive surveillance programs (19).

Not only is it important to examine adherence and uptake of surveillance testing, but reasons for lack of uptake must be explored. Although our surveillance protocol was not particularly onerous on patients, and was applied stringently by our health system, there was still a significant level of non-compliance due to patient factors. It is difficult to draw definitive conclusions on the reasons for this, and our study cannot fully quantify the proportion of non-compliance that is related to patient factors. We did however find that older age groups were less likely to adhere to routine recommended surveillance, which is consistent with prior studies (29-32). Our findings were comparable to the literature for those with increased comorbidities, who were less likely to receive surveillance testing (32). This was also the case for those with higher staged cancers. While no disparities were identified for people of non-English speaking backgrounds, nor did a patient's sex play a role in uptake of surveillance, we did not perform bioequivalence tests and hence cannot make definitive conclusions regarding absence of effects. Reassuringly, the fact that no significant disparities were found for patients of non-English speaking backgrounds highlights that our current surveillance system of involving health care workers and interpreters, may be useful in reducing potential inequalities in care, or may have contributed to similar

levels of compliance as for English speaking patients. Surveillance testing was also equitable across sociodemographic groups and geographical location, with no variations identified for uptake of first CT CAP and colonoscopy which were both provided by our own institution. This is in contrast to the findings of other Australian and international studies that report variations in care based on geographical location (23, 29, 33). We do acknowledge that socioeconomic status and geographic location are not necessarily comparable.

Overall, the primary aim of colorectal cancer surveillance is to detect recurrence of disease or new pre-malignant lesions in the colon at a stage where potentially curative treatment is possible, thereby improving patient survival (25, 31). At present, little is known about the uptake of surveillance and patterns of survivorship care in Australia. Young et al. were the first to explore this, albeit in the form of a patient survey which is limited by patient recall and selection bias (23). To our knowledge, our study is the first retrospective cohort study to explore the uptake of surveillance by patients treated for colorectal cancer in Australia. We showed that there is an under-utilisation or delay in surveillance testing by some patients, and the reasons for this are likely to be multifactorial in nature. We believe that main causes of our findings is firstly the lack of resources to be able to provide patients timely access to appointments and secondly the absence of a system that can track patient appointments and investigations to ensure that they are completed in a timely manner, notifying clinicians when this does not occur. For us locally, a potential solution to improve on our results would be to develop within our Electronic Medical Records (EMR) a system to "real time" track these patients which will automatically request and highlight patients who are not adhering to their surveillance program. Alternatively, adherence to surveillance testing could be improved on by the provision of survivorship care plans to all patients, a recommendation endorsed by the Institute of Medicine (34). There is strong support for the development and use of survivorship care plans for cancer survivors, with studies showing that patients who are linked back with their primary care providers, have identical outcomes to those treated in the hospital setting (35-38). An alternate strategy would be to employ dedicated survivorship care nurses, which has been successfully utilised in prostate and breast cancer care (39, 40).

This study has several limitations. It is a retrospective cohort study and as such, results are dependent on the quality of the original raw data and how the data were extracted. However, all patients treated by colorectal cancer surgery were included in our prospectively maintained registry. While our study is essentially an audit of our institution's compliance to surveillance protocols, its strengths lie in the fact that we are reporting on adherence to a common practice of colorectal cancer surveillance in a large cohort from a diverse background. These results will help other institutions with a similar patient background in a climate of reduced available resources. Other limitations of our study include the fact that patients included in our study could have completed part of their follow-up elsewhere (i.e. primary care physician) and such events were not recorded in our institutions' records, leading to under-reporting of follow-up. Unfortunately, there is no way to assess the proportion of cases where part of the surveillance occurred elsewhere as this would have strengthened our study. In the use of administrative records, it is extremely difficult to define and determine reasons for lack of adherence to guidelines as these are likely to be multifactorial. Although our study only examined the first two years of follow-up, there is significant information we have identified which we can use to address our current practice. Problems include lack of awareness of institutional guidelines by new or junior doctors, or poor understanding by patients for the need to adhere to appointments. Although a standardised protocol is being used at our institution, we lack a reliable mechanism to track patients' follow-up. In addition, reasons for deviation from planned surveillance may be linked to system factors at the hospital or health service level. While these results are useful in targeting groups that need to be prioritised for surveillance, more research is needed to identify modifiable patient risk factors as well as healthcare and institutional factors which may impact on the uptake of colorectal cancer surveillance. However, we feel that the results of our study can be very beneficial to other institutions both locally and internationally in helping them identify factors which may be affecting their surveillance program. Finally, while our study examined uptake of surveillance, it did not examine differences in adenoma detection or colorectal cancer recurrence rates in those who were more compliant with surveillance testing compared to those who were not. Although this study is non randomised, there is an opportunity to examine this in future studies by our group.

CONCLUSION

Our study provides a useful insight into the uptake of surveillance by patients treated for colorectal cancer in a large tertiary centre in Australia. Despite an idealised protocol of surveillance being in place, this was inconsistently applied across our patient cohort. As our data is from a prospectively managed colorectal cancer registry, it has allowed us to accurately identify the areas of weakness which we believe is common within Australian public institutions and our findings can be applied to help improve on surveillance in other international centres. Our study highlights that despite having clinician provided colorectal cancer surveillance follow up, patients still had a large variation in their time to surveillance investigations and the reasons for this are likely to be multifactorial in nature. Poor uptake of surveillance testing was more prevalent in patients from older age groups, those with multiple co-morbidities, and higher stage cancers. Further work is required to explore modifiable factors for reduced surveillance in order to provide improved survivorship care in "at risk" individuals. Once identified, initiatives can be developed to ensure equitable access to surveillance testing. Moreover, further research is required to determine the most optimal methods and timing of surveillance in this vulnerable patient population.

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Table 1. Sociodemographic and tumor characteristics (n = 675)

CHARACTERISTIC		n (%)
Gender	Male	387 (57.3)
	Female	288 (42.7)
Mean age in years ±SD		66.7 ± 12.3
SEIFA score †	1	181 (26.8)
	2	106 (15.7)
	3	158 (23.4)
	4	166 (24.6)
	5	64 (9.5)
Primary Language	English	514 (76.1)
	Non-English	161 (23.9)
ASA ‡	1	34 (5.0)
	2	290 (43.0)
	3	273 (40.4)
	4	29 (4.3)
	Not recorded	49 (7.3)
ACPS Staging §	A	147 (21.8)
	B	225 (33.3)
	C	193 (28.6)
	D	71 (10.5)
	Not recorded	39 (5.8)

SD = standard deviation

SE = standard error

†**SEIFA score** = Index of relative socio-economic disadvantage which is a general socio-economic index measured out of five. A score of 1 suggests more disadvantage, while a score of 5 reflects less disadvantage (9)

‡ **ASA** = American Society of Anesthesiologists score (6)

§**ACPS** = Australian Clinicopathological Staging System (7)

Figure 1 - Kaplan Meier graph showing time to first Computed Tomography of Chest, Abdomen and Pelvis (CT CAP). - - - median time to first CT CAP; shaded areas 95% confidence intervals

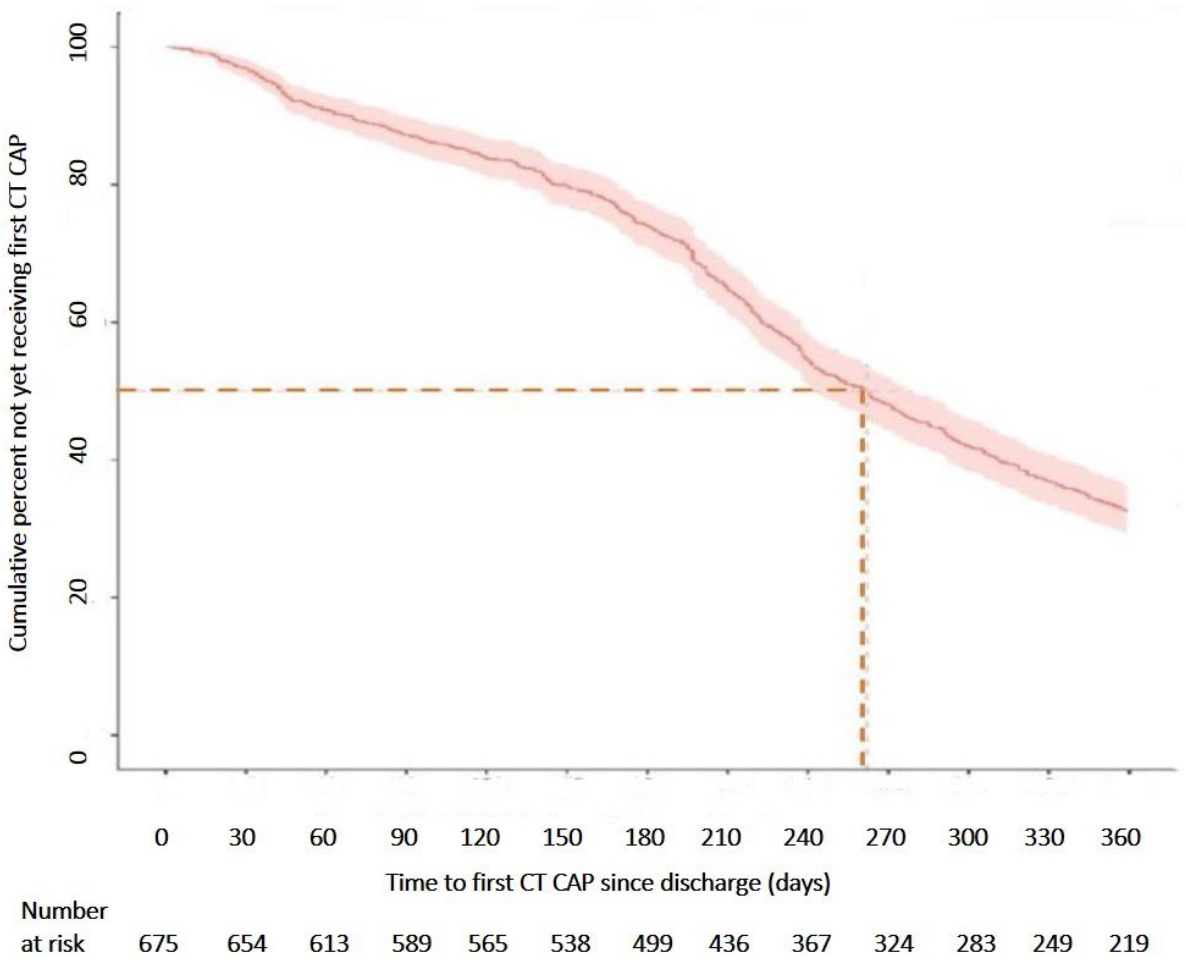

Figure 1. Kaplan Meier graph showing time to first Computed Tomography of Chest, Abdomen and Pelvis (CT CAP). ---- median time to first CT CAP; shaded areas 95% confidence intervals

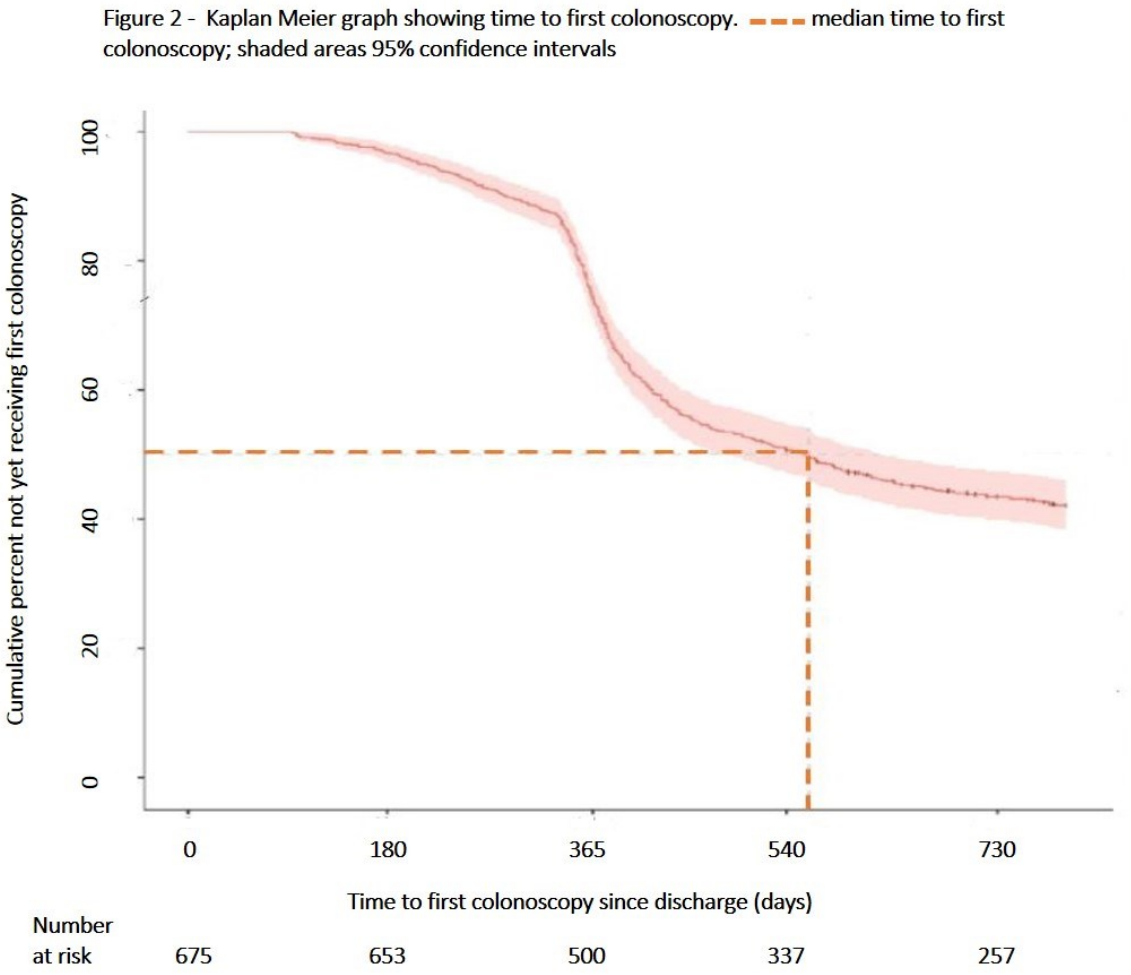

Figure 2. Kaplan Meier graph showing first colonoscopy. ---- median time to first colonoscopy; shaded areas 95% confidence intervals

GRAPHICAL ABSTRACT

Our study provides a useful insight into the uptake of surveillance by patients treated for colorectal cancer. Despite an idealised protocol of surveillance being in place, this was inconsistently applied. Poor uptake of surveillance testing was more prevalent in patients from older age groups, those with multiple co-morbidities, and higher stage cancers but reassuringly, no differences were found with respect to those from non-English speaking backgrounds, sex and lower socioeconomic status.