Cancer pathways are associated with improved long-term survival

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ABSTRACT

INTRODUCTION: The impact of cancer patient pathways (CPP) on long-term outcome after surgery for colorectal cancer has not been documented. This study aimed to investigate the effect of CPP on survival in patients who underwent surgery for colorectal cancer.

METHODS: This was a retrospective cohort study performed in a single centre on prospectively collected data from a national database, the Danish Colorectal Cancer Group. In total, we reviewed 309 consecutive patients (145 females) with a median age of 70 years (range: 30-92 years), who underwent surgery for colorectal cancer between 2007 and 2009.

RESULTS: A total of 148 patients who underwent elective surgery after the introduction of CPP on 1 April 2008 had a decrease in the median number of days from referral to endoscopy (from 8 to 6, p = 0.001) and from referral to oncological treatment (from 46.5 to 32 days, p < 0.001) and from referral to surgery (from 28 to 22 days, p = 0.066), but this latest reduction was not significant. Overall survival (OS) was analysed using the Kaplan Meier method; and variables were compared with the log rank test. The 60-month OS was significantly improved from 61.1% in those who were operated before 1 April 2008 (n = 161) to 72.6% in the CPP group operated after 1 April (p = 0.026). Using the Cox regression model, we found that CPP was an independent factor associated with survival (p = 0.032, hazard ratio: 0.661, 95% confidence interval: 0.454-0.964).

CONCLUSION: Introduction of CCPs in a single centre was associated with a significant improvement of overall survival, and using Cox regression we found that the CPP was an independent marker for survival. Larger studies are needed to clearly understand the effect of CPP.

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In 2011, the incidence of colorectal cancers registered in the national database, the Danish Colorectal Cancer Group (DCCG), was 3,974 [1, 2].

Five-year survival in Denmark has improved from 48.2% in 1995-1999 to 55.8% in 2005-2007 in patients with colorectal cancer. These results were inferior to those from Norway (62.0%) and Sweden (62.6%) in 2005-2007 [3]. Based on these results, national cancer plans were prepared in the years 2000 and 2005. In the autumn of 2007, a political decision was made to improve treatment of patients with suspected cancer through the introduction of cancer patient pathways (CPP) in Denmark [4].

The purposes of the CPP were to optimize patient treatment by reducing referral time and thereby improving the prognosis [5, 6]. It has been shown that the introduction of multi-disciplinary team (MDT) meetings regarding patients with lung cancer and rectal cancer improve survival [7-9]. Since 2006, MDT meetings have been mandatory when treating patients with colorectal cancer in Denmark.

In the UK, a two-week wait from referral to colonoscopy has been the norm since 2001. Results from retrospective studies have shown a reduced waiting time which is thought to be psychologically beneficial to patients and, also, cost-effective [10, 11]. Other results from the two-week referral included an increase in number of advanced cancers detected [12]. The rapid referral pathway for suspected colorectal cancer in Madrid (Spain) was associated with a reduction in waiting time to colonoscopy and an increase in the diagnosis of early cancer [13]. Two studies from the UK reporting overall five-year survival found no significant improvement in the groups with two-week waiting time from referral to colonoscopy [14, 15].

A report based on data from the Danish Cancer Registry found an improved one-year survival in patients with colorectal cancer when comparing patients treated in the 2004-2006 period with patients treated in the 2007-2009 period. This finding leads to speculation as to whether this result may be related to the national cancer plans and perhaps, in particular, to the CPP [16]. Thus, the aim of this study was to evaluate the effect of CPP in patients with colorectal cancer using long-term overall survival as the primary endpoint. The secondary outcomes were time from referral to colonoscopy, surgery and oncological treatment, respectively.

METHODS

The patients were found using the national database operated by the DCCG. Patients diagnosed with colonic and rectal cancers in Denmark from February 2001 were included [2]. A search in this register was conducted and included patients all diagnosed with and treated for

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TABLE 1

Patients demographics, non-cancer patient pathway and cancer patient pathway.

	Non-CPP patients	CPP patients	p-value
Patients, n	161	148	-
Gender, n			
Female/male	73/88	72/76	0.570
Age, years, median (range)	70 (36-92)	71 (30-91)	0.229
ASA score, n (%)			0.901
1	28 (17.4)	28 (18.9)	
2	88 (54.7)	78 (52.7)	
3	44 (27.3)	40 (27.0)	
4	1 (0.6)	2 (1.4)	
Tobacco, n (%)			0.314
Never	58 (36.0)	54 (36.5)	
Ongoing	27 (16.8)	34 (23.0)	
Previously	76 (47.2)	60 (40.5)	
Rectum/colon, n	54/107	51/97	0.526
UICC stage, n (%)			0.849
1	23 (14.3)	25 (16.9)	
2	60 (37.3)	58 (39.2)	
3	58 (36.0)	48 (32.4)	
4	20 (12.4)	17 (11.5)	
Oncological treatment, n			
Yes/no	79/82	66/82	0.431
From referral to, days, median (range)			
Endoscopy	8 (5-35)	6 (2-23)	0.001
Surgery	28 (7-73)[a]	22 (5-35)[a]	0.066
Oncology	46 (16-105)	32 (15-95)	< 0.001

ASA = American Society of Anesthesiologists; CPP = cancer patient pathways; UICC = Union Internationale Contre le Cancer.
a) In patients who underwent long radiotherapy the time period is calculated from the end of radiation therapy to surgery.

colorectal cancer at Slagelse Hospital from February 2001 to February 2012, a total of 1,877 patients. To insure a homogeneous group regarding surgical treatment, surgeon, radiation therapy and chemotherapy, patients who underwent surgery and were referred to our institution one year before and one year after the introduction of CPP were included in the present study. Patients who underwent emergency surgery during the study period were excluded. At the time of investigation, no patients were treated with laparoscopic surgery, and the Department of Surgery had not introduced fast-track surgery [17]. In total, 309 patients met the inclusion criteria. This patient cohort was analysed to establish whether the introduction of CPP had improved survival. The DCCG has a completeness of surgical data of 96.4% [1]. Since this study was based on the national DCCG database, which is already approved by the local ethics committee, no further approval was needed and informed consent from the patients was not required.

A total of 145 patients had oncological treatment with chemotherapy or radiotherapy. In all, 82 received adjuvant chemotherapy (oxaliplatin and capecitabin) after primary resection. Another group of patients with inoperable tumours were referred for palliative oncological treatment (n = 37), including fluorouracil, CPR-11, irinotecan, capecitabin, oxaliplatin, bevacizumab. A total of 22 patients with low rectal cancer were allocated for neoadjuvant radiotherapy prior to surgery. Treatment decisions were based on clinical assessment, the pathology report and computed tomography (CT)/magnetic resonance imaging (MRI) presented at the MDT meetings.

Implementation of the colorectal cancer patient's pathway

Introduction of CPP in our department was done in accordance with national guidelines. The department of surgery had to improve outpatient clinic facilities, but no additional doctors were employed. The main changes associated with reorganisation of clinical work were seen in the Department of Radiology and the Department of Pathology.

Outpatient clinic

At the outset, extra capacity was needed in the endoscopy and outpatient clinics. Subsequently, three extra nurses were employed to assist with endoscopy and the outpatient clinic. Two additional secretaries were needed for coordination of MRI, CT, histology and the booking of patients in the outpatient clinic. One secretary was in charge as *pathway coordinator* to ensure that patients did not wait longer than needed and to book MDT meetings and register data in the DCCG database.

Department of Radiology

The Department of Radiology operated with a maximum waiting period of one week for MRI, CT or ultrasound. When possible, examinations were rescheduled for other nearby hospitals to meet the criteria. No extra radiologists were employed, but ten extra radiographers were employed to cope with the additional workload.

Department of Pathology

The Department of Pathology aimed to conclude 90% of pathology reports from endoscopic biopsies within four days, and to finish the colon or rectal specimen seven days after surgery.

To meet the increased productivity requirements, one-and-a-half laboratory technicians were employed, and equipment accelerating the fixation rate in the tissue was acquired. A lean project was conducted to improve routines, and a new method to colour the specimen (Phil Quirke) was implemented routinely, according to international standards. An employee with IT skills was needed to ensure that the "time frame" was kept,

and to check procedures according to the department's standards.

Statistics

Demographic differences between patient groups were compared using the chi-square test and the independent t-test in order to test for equal distribution between control and case group. Patient survival was calculated from Kaplan-Meier survival estimates and log rank. Cox regression analysis was calculated to find the independent factor of survival. Factors used for analysis in the Cox regression were CPP, age, gender, colon/rectum, Union Internationale Contre le Cancer (UICC) stage ≤ 2/> 3, American Society of Anesthesiologist (ASA) score ≤ 2/> 3 and received adjuvant or palliative oncological treatment post-operatively (yes/no). Cox regression was used to discriminate between these factors as independent factors of survival with a FORWARD and BACKWARD test. Statistical tests were considered significant if $p < 0.05$. Statistical analysis was performed using a statistical software package (SPSS, version 19.0).

Trial registration: not relevant.

RESULTS

A total of 309 patients were diagnosed with and treated for colorectal cancer with elective surgery at Slagelse Hospital from 1 April 2007 to 31 March 2009. In all, 204 patients had colonic cancer and 105 had rectal cancer. The Department of Surgery, Slagelse Hospital, started the colorectal CPP on 1 April 2008. The 161 patients diagnosed from 1 April 2007 to 31 March 2008 were considered to be in the control group (non-CPP) and the 148 patients diagnosed from 1 April 2008 to 31 March 2009 were in the case group (CPP group). No significant differences were found between the two groups regarding type of cancer, ASA classification and UICC tumour stage or in the number of patients undergoing oncological treatment, see Table 1.

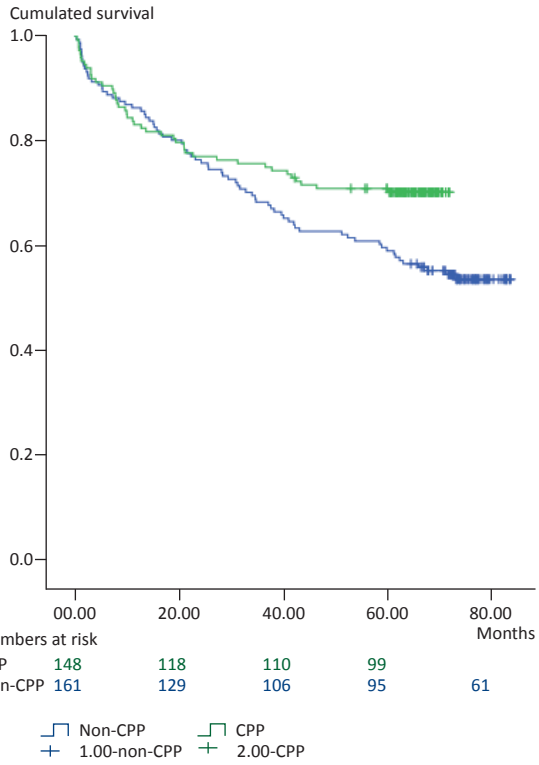
The median referral time from GP to endoscopy improved significantly from eight days to six days. The time from referral to oncological treatment improved significantly from 46.5 days to 32 days. Time from referral to surgery was reduced from 28 days to 22 days after the introduction of the colorectal cancer patient pathway, although this was non-significant. The time from referral to surgery also included the patients with rectal cancer who underwent radiation therapy for five weeks + six weeks of waiting time prior to surgery, but this was excluded in the calculation, **Table 1**.

Figure 1 shows a significant improvement of the long-term survival rate from 61.1% to 72.6% after the introduction of the CPP (p-value 0.026).

Cox regression analysis FORWARD and BACKWARD showed similar results. Being a part of the CPP group was an independent factor of survival with a hazard ratio of 0.661, 95% confidence interval: 0.454-0.094, p = 0.032. Other independent factors of survival were age ≤ 70 years, UICC ≤ 2, no oncological (adjuvant or palliative chemotherapy) treatment post-operatively and being female (**Table 2**).

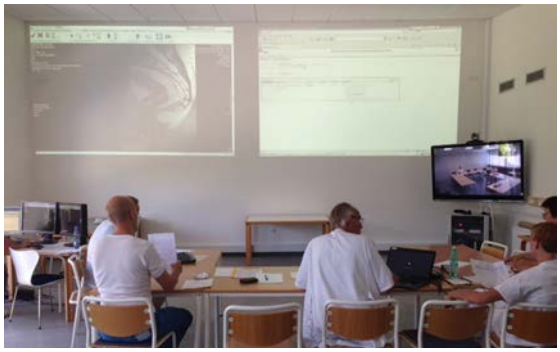
FIGURE 1

Kaplain-Meier plot showing the survival of both non-cancer patient pathways (non-CPP)- and CPP patients. The five-year survival was 61.1% for non-CPP patients and 72.6% for CPP patients log rank test: p = 0.026.



DISCUSSION

In this study we found a significantly longer overall survival in patients with colorectal cancer after introduction



Multidisciplinary team meeting with surgeons, pathologist, radiologist and oncologist live from Næstved.

TABLE 2

The association of independent factors with overall survival determined by the Cox hazard risk model after FORWARD and BACKWARD analysis.

	HR	95% CI	p-value
Part of CCP, yes/no	0.661	0.454-0.964	0.032
Age, ≤ 70 yrs/> 70 yrs	0.361	0.222-0.523	< 0.001
UICC stage, ≤ 2/> 2	0.341	0.217-0.499	< 0.001
Oncology, no/yes	0.601	0.396-0912	0.017
Gender, male/female	2.770	1.087-2.300	0.016

CI = confidence interval; CPP = cancer patient pathways; HR = hazard risk; UICC = Union Internationale Contre le Cancer.

of CCPs, from 61.1% to 72.6% at five years. The Cox regression analysis recognised CPP as an independent factor of survival together with age, UICC, gender and no chemotherapy post-operatively. Other factors such as ASA group and tumour site were not independent factors of survival in this study.

The main difference between the two groups (CPP/non-CPP) was the time from referral to colonoscopy and from referral to chemotherapy. It was previously described in the literature that delay influences survival [5, 6] and that a longer time from surgery to adjuvant chemotherapy, exceeding four weeks, was associated with poorer survival (14% decrease of OS) among patients with colorectal cancer [18, 19]. The Kaplain-Meier plot of the two groups starts to deviate only until after 20 months. This is different to the conclusions made by Storm et al [16], who observed the effect at the one-year follow-up.

In the study design, we have tried to exclude differences in the management of the patients with regard to type of chemotherapy, MDT meetings, fast track surgery and open surgery. The use of bevacizumab was introduced for palliative patients late in this study period, but its effect is limited [20], and only 12% (37/309) of the patients were eligible for this treatment in the CPP group and this explanation, for the improvement seen in our study, can therefore be discarded. Another reason for improved survival after the introduction of faster referrals would be change in tumour stage, which was the case in a study from Spain [13]. In our study, no change in UICC classification towards early cancer detection was found.

The two weeks of waiting time introduced in the UK are very different from the CCP regarding the way referrals are organised [14, 15]. The two-week waiting time is primarily a way to reduce time from referral to colonoscopy, whereas the CPP is a system to improve time from referral to endoscopy, surgery and oncology, respectively. To meet the recommendations of the CPP with regard to shorter waiting time to endoscopy, surgery and oncology, substantial changes were made in the organisation of several departments at the hospital. The reorganisation took place in the Department of Surgery in the Out-patient clinic and Endoscopy; in the Department of Pathology to reduce time to pathology report to four days; in the Department of Radiology to perform CTs within seven days and, finally, in the Department of Oncology to improve time to chemotherapy. Most of these changes do not form part of the two-week waiting time-initiative in the UK. Schneider et al showed no significant improvement in five-year survival after introduction of the two-week waiting time from 41.5% to 52.6% [14], and Zafar et al also showed no significant improvement in five-year survival (71% to 72%) after introduction of two weeks of waiting time [15]. Besides the above described reorganisation of several departments, the difference between our study and that of Schneider et al and Zafar et al is the number of patient included, 189 and 148 versus 309 in our study. With more patients in our study, the power improves, and this power would have changed the result in Schneider et al toward a significant improvement after the introduction of two-week referral.

Schneider et al used a case group which meets similar criteria to those of the CPP. The non-CCP was from outpatient referral. This selection may have had an impact on the outcome. Some disadvantages with confounders may be evident when using a historical control group, as was the case in Zafar et al and in the present study [14, 15]. A known confounder with a historical control group is the fact that with time improvements in survival are seen. This improvement in survival carries the risk of positive results and false conclusions. We have tried to limit this confounder by including patients only from one year before and one year after the introduction of CPP.

Zafar et al looked at elective and curative surgery and excluded patients who died within the first 30 days post-operatively, which increased survival to over 70% [15]. We included palliative patients and reached an overall 60-month survival of 72.6% after the introduction of CPP.

Our study supports the conclusion that CPP has improved survival in patients with colorectal cancer. This study lacks randomisation and prospective study design; still, we found that the introduction of the colorectal CPP in a single colorectal centre improved the long-term survival significantly. The Cox regression analysis identified CPP as an independent factor for survival. The introduction of CPP has significantly reduced the time from referral to endoscopy and oncology. Further studies and more data are needed to secure these findings.

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