Original Research

Adjuvant chemotherapy and relative survival of patients with stage II colon cancer — A EURECCA international comparison between the Netherlands, Denmark, Sweden, England, Ireland, Belgium, and Lithuania

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Abstract  Background: The aim of the present EURECCA international comparison is to compare adjuvant chemotherapy and relative survival of patients with stage II colon cancer between European countries.
Methods: Population-based national cohort data (2004–2009) from the Netherlands (NL), Denmark (DK), Sweden (SE), England (ENG), Ireland (IE), and Belgium (BE) were obtained,
chemotherapy; Surgery; International comparison; Population-based

Results: Overall, 59,154 patients were included. The proportion of patients receiving adjuvant chemotherapy ranged from 7.1% to 29.0% (p < 0.001). Compared with NL, a better adjusted relative survival was observed in SE (stage II: relative excess risks (RER) 0.53, 95% confidence interval (CI) 0.44–0.64; p < 0.001), and BE (stage II: RER 0.84, 95% CI 0.76–0.92; p < 0.001), and in IE for patients with stage IIA disease (RER 0.80, 95% CI 0.65–0.98; p = 0.03).

Conclusion: The proportion of patients with stage II colon cancer receiving adjuvant chemotherapy varied largely between seven European countries. No clear linear pattern between adjuvant chemotherapy and adjusted relative survival was observed. Compared with NL, SE and BE showed an improved adjusted relative survival for stage II disease, and IE for patients with stage IIA disease only. Further research into selection criteria for adjuvant chemotherapy could eventually lead to individually tailored, optimal treatment of patients with stage II colon cancer.

1. Introduction

Colorectal cancer is the third most common cancer in males and the second in females, and it is the second cause of cancer death in Europe. In total, 447,000 new cases and 215,000 deaths are estimated to have occurred in 2012 [1]. Approximately 70% of patients with colorectal cancer have a tumour in the colon [2]. Surgery is the mainstay curative treatment for colon cancer. Depending on stage, surgery may be followed by adjuvant chemotherapy with the aim of eradicating micrometastases.

The role of adjuvant chemotherapy in patients with stage III colon cancer is well established, resulting in a reduction in recurrence rate and an improvement in survival [3–9]. Nowadays, oxaliplatin combined with capecitabine or 5-fluorouracil (FU)/leucovorin (LV) is standard in the adjuvant treatment of stage III colon cancer [10–12].

On the contrary, the role of adjuvant chemotherapy in patients with stage II colon cancer remains uncertain despite several randomised controlled trials (RCTs) exploring this subject [13]. Currently about 15% of patients with stage II colon cancer will develop metastatic disease within 5 years after diagnosis of the primary tumour [14]. According to the ESMO Clinical Practice Guidelines, adjuvant chemotherapy could be considered in patients with high-risk stage II colon cancer defined as at least one of the following characteristics: poorly differentiated tumours, pT4 disease, vascular or lymphatic or perineural invasion, obstruction or perforation, and fewer than 12 lymph nodes sampled [12].

Previous studies have shown that colon cancer survival significantly varies across Europe, with the lowest relative survival in Eastern Europe [15,16]. These differences in relative survival might be partly attributable to differences in patterns of care among European countries.

Although RCTs are considered to be the gold standard for evaluating the effectiveness of interventions, they are costly, time consuming, not always feasible, and importantly, results cannot be extrapolated to the general population [17]. Besides, RCTs in stage II colon cancer did not give conclusive evidence concerning the effectiveness of adjuvant chemotherapy so far. As an alternative, comparative effectiveness research with large, ideally population-based, datasets could provide clues for optimal treatment strategies.

The aim of the present EURECCA international comparison is to compare the use of adjuvant chemotherapy and to compare relative survival of patients with stage II colon cancer between European countries.

2. Patients and methods

2.1. Patients

National datasets from the Netherlands Cancer Registry (NL), the Danish Colorectal Cancer Group database (DK), the Swedish Colorectal Cancer Registry (SE), the English National Cancer Registration Service database Cancer Analysis System (ENG), the National Cancer Registry Ireland (IE), and the Belgian Cancer Registry (BE) were included. Moreover, we obtained single-centre data from the Hospital of Lithuanian University of Health Sciences Kaunas Clinics (LT).

We selected all patients with stage II colon cancer (ICD-10 C18), who were diagnosed between 2004 and 2009, except for patients from SE who were diagnosed between 2007 and 2009. All patients were surgically treated with curative intent.
We collected information on gender, age, year of incidence, TNM stage, tumour grade, use of adjuvant chemotherapy, and vital status at date of last follow-up. Age was categorised as <65 years, 65–74 years, and ≥75 years. The information on tumour stage was based on pathological reports (pTNM). If pathology data were missing, clinical tumour stage was used. The TNM classification 5th or 6th edition was used for staging. Stage was subclassified as IIA (T3N0M0; tumour invades through the muscularis propria into the subserosa or into non-peritonealised pericolic tissue, no regional lymph node metastasis, no distant metastasis) or IIB (T4N0M0; tumour directly invades other organs or structures, and/or perforates visceral peritoneum, no regional lymph node metastasis, no distant metastasis). No substage was available for ENG. Tumour grade was classified as grade I (well differentiated), grade II (moderately differentiated), grade III (poorly differentiated), and grade IV (undifferentiated/anaplastic). Adjuvant chemotherapy was defined as ‘no’ or ‘yes’. For ENG, adjuvant treatment was defined as yes if a patient had surgery followed by chemotherapy, and as ‘unknown’ if a patient had surgery and no record of receiving chemotherapy after surgery, due to incomplete data on treatment.

2.2. Statistical analyses

Median follow-up was calculated according to the reverse Kaplan–Meier method [18]. The analyses were done for all patients with stage II colon cancer, as well as stratified by stage (IIA, IIB) excluding ENG.

We performed crude and adjusted logistic regression models to compare the proportion of adjuvant chemotherapy between the countries. Time of follow-up was calculated from date of surgery until death, or until end of follow-up (censored). Relative survival was calculated by the Ederer II method [19] as the ratio of the survival observed among the patients with stage II colon cancer and the survival that would have been expected based on the corresponding general population (matched by country, age, gender, and year of diagnosis). National life tables from www.mortality.org were used to estimate expected survival. Relative excess risks (RERs) of death were estimated using an adjusted generalised linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. The country with the lowest proportion of patients receiving adjuvant chemotherapy was used as reference category.

Countries with national data were compared: NL, DK, SE, ENG, IE, and BE. Single-centre data from LT were used to describe patient characteristics and the proportion of patients receiving adjuvant chemotherapy, but not to calculate relative survival. The analyses were adjusted for potential confounders: gender, age (continuous), and year of incidence. No information on tumour grade was available for DK. Therefore, we did not adjust for tumour grade in the adjusted logistic regression models used to compare the proportion of patients receiving adjuvant chemotherapy between the countries. However, we adjusted for tumour grade in the relative survival analysis for all countries with national data except DK.

Sensitivity analysis was performed including patients who were diagnosed between 2007 and 2009. A p-value of <0.05 was considered as statistically significant. Analyses were performed with IBM SPSS Statistics 20.0 and STATA SE 12.0.

3. Results

In total, 59,154 patients were included: 14,217 patients from NL, 4575 patients from DK, 3467 patients from SE, 26,075 patients from ENG, 2415 patients from IE, 8232 patients from BE, and 203 patients from LT. Patient and tumour characteristics are listed in Table 1. Median follow-up was 6.7 years (interquartile range 5.1–8.3).

3.1. Stage II colon cancer

Fig. 1a shows the proportion of patients receiving adjuvant chemotherapy and the adjusted RERs by country. The proportion of patients receiving adjuvant chemotherapy varied from 7.1% in NL to 29.0% in BE (adjusted \( p < 0.001 \)). No clear linear pattern was observed between adjuvant chemotherapy and adjusted RERs of death.

Five-year relative survival with 95% confidence intervals (CIs) are listed in Table 2. Compared with NL, a better relative survival was observed in SE as demonstrated by a RER of 0.53 (95% CI 0.44–0.64; \( p < 0.001 \)), and BE (RER 0.84, 95% CI 0.76–0.92; \( p < 0.001 \)) after adjustment for potential confounders (Fig. 1a; Table 2).

Sensitivity analysis including patients diagnosed between 2007 and 2009 showed similar results except for BE (adjusted RER 0.88, 95% CI 0.76–1.01; \( p = 0.06 \)). Compared with NL, a better relative survival was observed in SE (adjusted RER 0.56, 95% CI 0.46–0.69; \( p < 0.001 \)).

3.2. Stage IIA colon cancer

The proportion of patients with stage IIA colon cancer receiving adjuvant chemotherapy ranged from 4.7% in NL to 25.1% in BE (adjusted \( p < 0.001 \)), whereas we did not observe a clear linear pattern between the use of adjuvant chemotherapy and adjusted relative survival expressed by RERs (Fig. 1b).

Five-year relative survival, as well as crude and adjusted RERs, is listed in Table 2. Compared with NL, a better adjusted relative survival was observed in SE (RER 0.45, 95% CI 0.34–0.61; \( p < 0.001 \)), IE (RER
0.80, 95% CI 0.65–0.98; p = 0.03), and BE (RER 0.80, 95% CI 0.71–0.90; p < 0.001).

Sensitivity analysis showed an adjusted RER of 0.76 (95% CI 0.59–0.97; p = 0.03) for DK, an adjusted RER of 0.73 (95% CI 0.51–1.03; p = 0.07) for IE, and an adjusted RER of 0.45 (95% CI 0.34–0.61; p < 0.001) for SE compared with NL.

3.3. **Stage IIB colon cancer**

The proportion of patients with stage IIB receiving adjuvant chemotherapy varied between 22.4% in NL and 49.4% in BE (adjusted p < 0.001). Again, no clear linear pattern was observed between use of adjuvant chemotherapy and adjusted RERs (Fig. 1c).

Table 2 lists the 5-year relative survival and crude and adjusted RERs for patients with stage II colon cancer receiving adjuvant chemotherapy between the NL, Denmark, Sweden (SE), ENG, IE, BE and LT. No clear linear pattern between adjuvant chemotherapy and adjusted relative survival was observed. However, both SE and BE showed an improved adjusted relative survival compared with the NL. In addition, IE showed an improved adjusted relative survival compared with the NL in patients with stage IIA disease.

The benefits of adjuvant fluoropyrimidine-based chemotherapy have been clearly demonstrated for patients with stage III colon cancer [3–7]. The MOSAIC trial found an improvement of 7.5% in 5-year disease-free survival and approximately 4% in 6-year overall survival with the addition of oxaliplatin to 5-FU/LV (FOLFOX) among patients with stage III colon cancer [9]. Moreover, the NSABP C-07 trial also demonstrated a benefit from the addition of oxaliplatin to 5-FU/LV for disease-free survival, although no significant benefit for overall survival was found [8]. Oxaliplatin combined with capecitabine showed similar results as oxaliplatin combined with 5-FU/LV [10]. As a result of these studies, oxaliplatin combined with capecitabine or 5-FU/LV is nowadays standard in the adjuvant treatment of stage III colon cancer [10–12].

For patients with stage II colon cancer, the role of adjuvant chemotherapy remains unproven. Several trials enrolled both patients with stage II and stage III disease, although the number of patients with stage II disease was much smaller than with stage III disease. Remarkably, most of these studies found a survival benefit of adjuvant chemotherapy in patients with stage III disease.
In a systematic review and meta-analysis, a better disease-free survival was found in patients with stage II colon cancer who were treated with adjuvant chemotherapy, while no improvement in overall survival was found [13]. On the contrary, a Dutch trial demonstrated improved overall survival for both stage II and stage III disease [20].

However, medical care has evolved since the above-mentioned trials have been performed. Over time, this has led to better outcomes for patients with colon cancer [15]. These better outcomes could be partly attributed to adjuvant chemotherapy, but also to other factors such as improved preoperative staging, surgery, pathology, and perioperative care [21–24]. Furthermore, stage migration may have occurred. Therefore, the absolute benefit of adjuvant chemotherapy under current circumstances is not known.

According to the ESMO Clinical Practice Guidelines, adjuvant chemotherapy should not be routinely administered to all patients with stage II colon cancer, but could be considered in patients with high-risk stage II colon cancer [25]. All countries included in this international comparison have incorporated this recommendation in their national guidelines. It is remarkable, as shown in our study, that the proportion of patients receiving adjuvant chemotherapy varies largely between these countries. This emphasises the variation in country-specific interpretation and considerations whether or not to start treatment. Moreover, the routine to identify high-risk patients may have been implemented differently among the countries. Further, patients’ reluctance to receive adjuvant chemotherapy may also vary across countries. Interestingly, a recent study by Verhoeff et al. including patients with high-risk stage
II colon cancer showed that patients with pT4 disease were more likely to receive adjuvant chemotherapy compared with patients with two or more high-risk factors, while patients with emergency surgery only, <10 lymph nodes evaluated only, or poor/undifferentiated grade only were less likely to receive adjuvant chemotherapy compared with patients with two or more risk factors. Moreover, patients aged <70 years, patients with a tumour in the distal colon, patients diagnosed in a more recent time period, and patients with less than two comorbid diseases more often received adjuvant chemotherapy [26].

Although survival of patients with colorectal cancer in Europe improved markedly over the past years, there are still significant differences in relative survival across Europe [15,16]. However, these studies lacked information on for example TNM stage and treatment. Several possibilities to explain the differences in survival have previously been suggested. These include demographic differences, differences in lifestyle, screening or diagnostic procedures, stage at diagnosis, health-care systems, and differences in access or use of effective treatment options [16].

In the current study, no clear linear pattern between adjuvant chemotherapy and relative survival was observed. However, we found that SE had a much better relative survival compared with the NL. Since we obtained data from SE for patients diagnosed between 2007 and 2009, we performed a sensitivity analysis including patients diagnosed between 2007 and 2009. These results also showed a better relative survival in SE for stage II (IIA and IIB together) and stage IIA, but the relative survival did not significantly differ for stage IIB disease. Relative survival differences between SE and the NL cannot solely be explained by the small difference in the use of adjuvant chemotherapy. The focus on improved colon cancer treatment on a national level since 2004–2005 in SE, including better preoperative work-up, improved surgery with the concept of complete mesocolic excision, less acute resections, and better pathology might at least partly explain the differences [27]. Moreover, other factors, not measured here, such as differences in health-care system will also play a role.

A better adjusted relative survival was also found for BE compared with the NL, except for stage IIB disease in the sensitivity analysis. On a scale from a low to a high proportion of patients receiving adjuvant chemotherapy, the NL and BE are two extremes. The large differences in adjuvant treatment might still partly contribute to the differences in relative survival between the NL and BE, although we found no clear linear pattern between adjuvant chemotherapy and relative survival.

Previous comparative studies showed relatively low survival for the United Kingdom [15,16]. However, in our study we did not observe this for ENG. It has been suggested that the relatively low survival in the United Kingdom could be due to late detection and diagnosis, access to treatment, especially to surgical treatment, and health inequalities [28,29]. Given that we selected patients with stage II colon cancer who were surgically treated with curative intent might be an explanation why we did not observe a worse relative survival for ENG. Moreover, it might be that ENG has different outcomes.
than the rest of the United Kingdom, although ENG comprises most of the area of the United Kingdom.

This study has some limitations. There might be unknown differences in data registration between the countries and completeness of vital follow-up. Although we adjusted the analyses for potential confounders, residual confounding by unmeasured factors cannot be entirely excluded due to the retrospective design of the study. For example, it is unknown what role differences in health-care systems between European countries play. Moreover, we had no detailed information on vascular or lymphatic or perineural invasion, obstruction or perforation, number of lymph nodes sampled, type or dose of chemotherapy, toxicity, chemotherapy compliance, comorbidity, life-style factors, performance, and quality of life, among others. As also stated by Storm et al., these variables should ideally be included in national population-based datasets to do more detailed analysis and to improve comparability between countries [30].

On the other hand, this study is unique in comparing both treatment and relative survival between European countries for a specific disease stage. Furthermore, we used a large dataset with almost 60,000 patients from seven countries. Importantly, national data covering the whole population were obtained for six of these countries. Single-centre data from LT were used to describe the proportion of patients receiving adjuvant chemotherapy, but not for relative survival analyses because these data might not be representative of the whole LT population.

In conclusion, the present population-based study, comparing both the use of adjuvant chemotherapy and relative survival of patients with stage II colon cancer between seven European countries, showed large differences in the proportion of patients receiving adjuvant chemotherapy. Moreover, no clear linear pattern between the use of adjuvant chemotherapy and relative survival was observed. Our findings should be a strong recommendation for further research into selection criteria for adjuvant chemotherapy. This could eventually lead to individually tailored, optimal treatment of patients with stage II colon cancer.

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Conflict of interest statement

We declare no competing interests.


