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Patterns of adjuvant chemotherapy for stage II and III colon cancer in France and Italy

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ABSTRACT

Background: European guidelines recommend adjuvant chemotherapy for stage III colon cancer but not for stage II.
Aim: To determine the extent to which adjuvant chemotherapy was used in Italy and France.
Methods: A common retrospective database of 2186 colon cancers diagnosed between 2003 and 2005 was analysed according to age, stage and presenting features.
Results: 38.9% of patients with stage II and 64.6% with stage III received chemotherapy in Italy, 21.7% and 65.1% in France. For stage II, the association between country and chemotherapy was only significant in patients diagnosed out of emergency ($OR_{Italy/France}$: 3.05 [2.12–4.37], $p < 0.001$) whereas patients diagnosed in emergency were as likely to receive chemotherapy in both countries. For stage III, there was a trend to a higher administration of chemotherapy for elderly patients in France compared to Italy. French patients were more likely than Italian to receive chemotherapy (OR: 1.91[1.32–2.78], $p = 0.001$).
Conclusion: Chemotherapy for stage III colon cancer was as extensively used in Italy as in France for young patients. Its administration could be increased in patients over 75. Stage II patients with a lower risk of relapse received chemotherapy more often in Italy than in France.

1. Introduction

The EUROCARE project was set up to measure international differences in cancer survival in Europe. The most recent data provided by EUROCARE 4 showed that colorectal survival varied across countries from 39.4% (Poland) to 58.2% (Switzerland) [1]. The quality of cancer treatment facilities, screening programmes, or evidence based guidelines may partly explain these differences. Access to adjuvant treatments may play a role to explain such discrepancies. Since the publication of trials in the beginning of the 1990s, adjuvant chemotherapy is recommended for stage III colon cancer in European guidelines [2]. It is associated with a nearly 10% crude survival improvement. For stage II colon cancer the benefits of adjuvant chemotherapy remain controversial. Although a large international multicentre pooled analysis of colon cancer trials failed to demonstrate a statistically significant benefit for stage II tumours [3], some experts advocate that chemotherapy may be effective for stage II patients at high risk of relapse, i.e. in case of locoregional extension, emergency, or insufficient number of examined nodes [2]. Nevertheless, European guidelines [2] and the American Society of Clinical Oncology panel [4], during the study period, did not recommend the routine use of adjuvant chemotherapy in stage II colon cancer.

The management of colon cancer in France and Italy is decentralised with multiple places of treatment and various specialists. It is not well known how adjuvant therapies have taken place at a population level. Population-based studies, recording all diagnosed cases in a well-defined population, represent the best way for checking the implementation of guidelines. Results have the advantage of not being affected by selection biases. However, such studies are difficult to perform because they require the active participation of the entire medical profession and reviewing the whole clinical information. Information on the management of cancers cannot be routinely collected by population-based cancer registries. Special surveys are required to collect data on a representative sample of incident cancer cases. Within the EUROCARE project and under the aegis of the "Groupe pour l'Epidemiologie et l'Enregistrement du cancer dans les pays de Langue Latine" (GRELL), we carried out a "high resolution" study using data collected by the network of French (FRANCIM) and Italian (AIRTUM) cancer

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Table 1
Description of the studied population.

	TNM stage II			TNM stage III		
	Italy *N* (%)	France *N* (%)	*p*	Italy *N* (%)	France *N* (%)	*p*
Males	403 (52.0)	224 (54.6)	0.388	336 (51.3)	182 (52.6)	0.695
Age						
0–64 years	217 (28.0)	93 (22.7)	0.085	216 (33.0)	81 23.4)	0.001
65–74 years	247 (31.9)	126 (30.7)		199 (30.4)	93 (26.9)	
75–84 years	249 (32.1)	146 (35.6)		183 (27.9)	134 (38.7)	
≥85 years	62 (8.0)	45 (11.0)		57 (8.7)	38 (11.0)	
Non-emergency	612 (81.7)	355 (86.6)	0.033	513 (81.2)	277 (80.8)	0.875
Resection with curative intent	715 (98.5)	390 (97.3)	0.002	603 (97.6)	318 (94.4)	<0.001
Chemotherapy administered	280 (38.9)	88 (21.7)	<0.001	395 (64.5)	224 (65.1)	0.859
0–11 examined nodes	257 (34.4)	129 (31.5)	0.310	210 (32.9)	98 (28.4)	0.150

registries. The objective of this study was to determine the extent to which adjuvant chemotherapy was used for patients with stage II and III colon cancer in Italian and French population during the period 2003–2005.

2. Patients and methods

2.1. Population

Data from 20 population-based cancer registries from Italy and France, retrospectively gathered in the context of the High Resolution EUROCARE-GRELL study, were analysed. In each registry, sample of colon cancer cases (C18 according to the ICD-10 classification) was randomly chosen in France on the basis of day and month of birth of patients and in Italy from the Italian Cancer Registries Association database [5] balancing for year of diagnosis was drawn up. For the present study, cancer of the rectum (C20), of the rectosigmoid junction (C19), anal cancers (C21) and non-epithelial colon cancers were excluded. The common database included 2186 adults (≥15 years) with colon cancer diagnosed and resected for cure in France in 2005 and between 2003 and 2005 in Italy.

2.2. Variables

A common protocol and data-checks provided the basis for data definition with appropriate quality and degree of completeness indicators. Four categories were assigned for age: <65, 65–74, 75–84, and over 85 years. Collected data included the clinical reasons for consultation (emergency for bowel obstruction or perforation or non-emergency) and the adjuvant chemotherapy administered. Information on the extent of the disease was based on pathology reports. Tumours were classified according to the TNM classification [6]. The following stages were defined: stage II including stage IIA (T3, N0, M0), IIB (T4, N0, M0) and stage III including IIIA (T1/2, N1, M0) and IIIB (T3/4, N1, M0) and IIIC (All T, N2, M0). Precise extension to colon wall was unknown for 2 stage II and 15 stage III colon cancers. Due to the small number of cases, IIIA and IIIB were grouped together. Resection was considered curative when the surgeon deemed the tumour completely removed with no microscopic evidence of spread to surgical margins and no evidence of distant metastases. The number of examined lymph nodes at the end of the resection was noted. Forty-five cases had unknown precise number of resected nodes (28 for stage II, 17 for stage III). Stage II colon cancer was considered at high risk of relapse in case of locoregional extension (IIB), emergency, or insufficient number of examined nodes (<12 examined lymph nodes).

2.3. Statistical analysis

At first, univariate analysis was performed. Associations between categorical data were analysed using a chi-square test for heterogeneity. The statistical significance level was set at $p = 0.05$ in a two-sided test. A logistic regression was used to estimate odds ratios (ORs) and their 95% confidence interval (CI), independently and significantly associated with the probability of receiving adjuvant chemotherapy. Age and sex were forced into the model. The other covariates were included in multivariate analysis if they were associated with the use of chemotherapy with $p < 0.20$ in the univariate analysis. Significance of the covariates was tested by likelihood ratio tests. Interaction terms were tested using a cut-off significance level of 0.15. Adjusted OR and 95% confidence intervals (CIs) were calculated. The analyses were performed using STATA^{TM}, release 11 (STATA Corp., College Station, TX).

3. Results

Table 1 shows the distribution of the cases in France and Italy according to studied variables (sex, age, presenting feature, adjuvant chemotherapy and number of examined nodes). Italian patients with colon stage II cancers were more often diagnosed in a context of emergency (18.3% vs. 13.4%). The percentage of Italian patients with colon stage III cancers belonging to early age groups was higher than that of French patients (63.4% aged under 75 vs. 50.3%).

Overall 38.9% of patients with stage II and 64.5% with stage III received chemotherapy in Italy. The corresponding proportions were 21.7% and 65.1% in France. Thus, no differences in proportion of administered chemotherapy in patients with stage III at diagnosis were seen between the two countries.

Focusing on the proportion of patients receiving chemotherapy in stage II and III colon cancers (Table 2), administration of chemotherapy decreased with growing age for both stages and both countries.

For stage II cancer, tumour extension did not influence the administration of chemotherapy, whereas a number of examined nodes higher than 12 were not only associated with a higher proportion of treated patients in Italy (42.2% vs. 33.2%) but also with a diagnosis in a context of emergency in France (45.5% vs. 17.9%). For stage III cancer, patients with advanced tumour extension (IIIC vs. IIIA/B) received more chemotherapy in Italy (70.9% vs. 61.5%). Presenting features out of emergency increased the proportion of Italian treated patients too (67.3% vs. 53.6%).

A multivariate regression model was used to identify the factors associated with chemotherapy (Table 3). After adjusting for age and sex, tumour extension was a significant factor influencing the administration of chemotherapy ($OR_{IIB\ vs.\ IIA} = 2.32$ [1.50–3.59], $p < 0.001$) for stage II colon cancer, whereas the number of