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Improvement in survival of metastatic colorectal cancer: Are the benefits of clinical trials reproduced in population-based studies?

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Abstract ***Aim of the Study:*** To describe trends in survival of non-resectable metastatic colorectal cancer (MCRC) over a 34-year period in a French population-based registry taking into account major advances in medical therapy.

Patients and Methods: 3804 patients with non-resectable metastatic colorectal cancer diagnosed between 1976 and 2009 were included. Three periods (1976–96, 1997–2004 and 2005–09) were considered.

Results: The proportion of patients receiving chemotherapy dramatically increased from 19% to 57% between the first two periods, then increased steadily thereafter reaching 59% during the last period ($p < 0.001$). Median relative survival increased from 5.9 months during the 1976–96 period to 10.2 months during the 1997–2004 period but, despite the availability of targeted therapies, remained at 9.5 months during the 2005–09 period. During the last study period, less than 10% of elderly patients received targeted therapies compared to more than 40% for younger patients. Their median relative survival was 5.0 months compared to 15.6 months in younger patients.

Conclusion: There was an improvement in survival in relation with the increased use of more effective medical treatment. However, at a population-based level, patients are not all treated equally and most of them, especially the elderly, do not benefit from the most up-to-date treatment options.

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1. Introduction

With more than 1,233,000 estimated new cases and 608,000 estimated deaths each year, colorectal cancer (CRC) is the third most frequent cancer and the second leading cause of cancer death worldwide.[1] Overall, an improvement in CRC survival has been observed over the last 25 years[2–4] mainly explained by a decrease in postoperative mortality and by an increase in the proportion of patients receiving surgery with curative intent, associated with an earlier diagnosis and the use of adjuvant chemotherapy for stage III tumours.[3,5,6] Approximately 20% of CRC patients present metastases at the time of diagnosis.[7] Phase III randomised clinical trials have shown a significant increase in the median overall survival of patients with metastatic CRC (MCRC), from less than 6 months when treated with intravenous 5FU only based regimen to more than 22 months in more recent trials using chemotherapy plus targeted therapy combinations, sequential treatment lines after a first progression and hepatic resection in selected patients.[8] It is not well known however how new treatments have spread at a population level, taking all institutions treating metastatic CRC into consideration. Community-based studies are needed to assess the use of medical treatments. Such studies are rare because they require the collection of detailed information which can seldom be collected by cancer registries. The aim of this study was to describe trends in survival of non-resectable synchronous metastatic CRC over a period of 34 years in a well-defined French population taking into account major advances in medical therapy.

2. Patients and methods

A population-based registry for digestive cancers was established in two administrative areas of Burgundy in France: Côte-d'Or (in 1976) and Saône-et-Loire (in 1982). It covers a resident population of 1,050,000 inhabitants, according to the 1999 census. Information on new cases is collected from public and private pathology laboratories, university and general hospitals, the regional cancer centre, private surgeons, oncologists, radiotherapists and gastroenterologists, general practitioners, Regional Health Service database, administrative hospital database and death certificates. No cases were registered according to death certificates alone, but these were used to identify missing cases. Because of the involvement of the entire medical profession and the multiplicity of information sources we can assume that nearly all newly diagnosed cases of colorectal cancer are recorded. The quality and completeness of the registry are certified every 4 years by an audit of the National Committee on population-based Registries.

Overall 4085 stage IV colorectal carcinomas (ICD-03 codes C18, C19 and C20) were newly diagnosed between 1976 and 2009. Among them, 281 had a primary R0 resection (6.3% during the 1976–1996 time period, 8.8% during the 2005–2009 time period), defined as a macroscopic resection of all malignant tissues and no microscopic evidence of surgical margin spread for both the primary tumour and synchronous metastatic tumour. These cases were excluded from the present analysis. Thus a total of 3804 cases were included. An active search for vital status was carried out for all patients using a standardised administrative procedure. Overall 41 patients (1.1%) were lost to follow-up within 3 years after diagnosis.

The administration of first line systemic treatments was routinely recorded. Information was unknown in 13 cases (0.34%). Standard chemotherapy regimens changed over time with the publication of randomised clinical trials and the approval of new drugs. Bolus 5-Fluorouracil (5FU) was the only treatment before 1997. Then infusional 5FU modulated by folinic acid (de Gramont regimen or Leucovorin and 5-Fluorouracil (LV5FU2) regimen) became the standard frontline option in 1997.[9] Rapidly, the benefit of adding irinotecan (irinotecan with fluorouracil and folinic acid (FOLFIRI) regimen)[10] or oxaliplatine (5-Fluorouracil, leucovorin and oxaliplatin (FOLFOX) regimen)[11] to 5FU-leucovorin was demonstrated. These regimens remained the standard treatment between 1997 and 2005 when antiangiogenic (bevacizumab[12]) and anti-epidermal growth factor receptor (EGFR) (cetuximab[13]) treatments became available. Taking into account this evolution and the successive market authorisation of drugs in France, the time at diagnosis was categorised into three periods (1976–1996; 1997–2004 and 2005–2009) for the present analysis.

Additional data have been included for the cases diagnosed since 2005 ($n = 789$) in order to collect data on comorbidities. Comorbidities were listed using the Charlson index.[14] The Charlson comorbidity index (CCI) score was calculated using the method previously reported by Charlson et al., in which each specific comorbid condition is weighted and scored proportionally to the disease-related risk of death irrespective of age. The CCI score was classified according to three groups: '0', '1' and '2+'. Comorbidities were unknown for eight cases.

2.1. Statistics

Relative survival estimates were based on excess mortality rate estimates in populations of patients with advanced colorectal cancers as compared with expected survival. Relative survival was estimated at 1 and 3 years by a classical method according to the likelihood maximum and modelled using excess mortality rate models with flexible parameters developed by Remontet et al.[15] Six candidate functions were investigated: regression cubic spline with two knots, regression cubic spline with one knot, cubic polynomial function, quadratic polynomial function, linear function and constant function.