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Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials ☆,☆☆

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Abstract ***Objective:*** To evaluate the impact on survival of primary tumour resection in patients with unresectable synchronous metastases from colorectal cancer (CRC).
Summary background data: Primary tumour resection in this setting remains controversial.
Patients and methods: We retrieved individual data of 1155 patients with metastatic CRC included in four first-line chemotherapy trials: Fédération Francophone de Cancérologie Digestive (FFCD)-9601, FFCD-2000-05, Actions Concertées dans les cancers COloRectaux et Digestifs (ACCORD)-13, and ML-16987. Patients with unresectable synchronous metastases were eligible for this study. We used univariate and multivariate analyses (Cox models stratified on the trial) to assess the impact of primary tumour resection and other potential prognostic variables on overall survival (OS) (the primary endpoint).
Results: Amongst the 1155 patients, 810 patients met the inclusion criteria and 59% ($n = 478$) underwent resection of their primary tumour, prior to trial entry (resection group). Compared

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to patients in the non-resection group ($n = 332$ [41%]), those in the resection group were more likely to have a colonic primary, lower baseline carcinoembryonic antigen (CEA) and alkaline phosphatase levels, and normal white-blood-cell count ($p < 0.001$ each). Primary tumour resection was independently associated to better OS in multivariate analysis (hazard ratio (HR), 0.63 [0.53–0.75]; $p < 0.001$, with a more favourable impact of resection on OS in case of rectal primary and low CEA level. Primary tumour resection was also independently associated to a better progression-free survival in multivariate analysis (HR, 0.82 [0.70–0.95]; $p < 0.001$).

Conclusion: Primary tumour resection was independently associated to a better OS in patients with CRC and unresectable synchronous metastases.

1. Introduction

Colorectal cancer (CRC) accounts for 1,234,000 new cases and 608,000 deaths each year in the world [1]. At the time of diagnosis, 20% of the patients have metastatic CRC (mCRC; stage IV disease). Approximately one-fifth to one-quarter of patients with mCRC can be resected in curative intent (primary tumour and metastases), either immediately or after chemotherapy, and may experience prolonged overall survival (OS) [2]. However, most patients with mCRC will never be amenable to curative-intent surgery. For these patients, the need for resection of the primary tumour remains a matter of debate, because the impact on OS is uncertain. Nevertheless, registry studies in the United States showed that 70% of patients diagnosed with stage IV CRC had undergone resection of their primary – thus mostly, for uncertain reasons, this rate is considerably higher than the rate of complications (e.g. bowel obstruction or perforation) related to the primary, with reported figures ranging from 13% to 20% [3–5].

The aforementioned registry studies both concluded that primary tumour resection was associated with a longer OS [3,4]. However, these registry studies were retrospective and had only access to the data collected in the registries – thus, no adjustments were possible for potential confounding factors. Other data available in the literature consisted mostly of small, retrospective surgical series, or focused on complications related to the primary rather than on the impact of primary tumour resection on OS [6–20].

To date, no trial randomised resection of the primary tumour versus no resection in patients with stage IV CRC. While awaiting the results of such trial, a possible alternative is to use individual data of mCRC patients included in chemotherapy trials to assess OS according to whether the primary tumour has been resected prior to trial entry or not [21]. Recently, we used this method with the individual patient data of the Fédération Francophone de Cancérologie Digestive (FFCD)-9601 trial [22], and found that primary tumour resection prior to trial entry was an independent predictor of longer OS and progression-free survival (PFS) in patients with CRC and unresectable synchronous metastases [23]. Nevertheless, these results were obtained in patients from a single trial, with low-efficacy, single-agent chemotherapy regimens.

The present study has three aims: to confirm the results, obtained in the FFCD-9601 patient population, in patients included in other trials and treated with oxaliplatin- or irinotecan-based chemotherapy with or without bevacizumab; to search for interactions between primary tumour resection and covariates on OS; and to assess the effect of resection on OS in the whole patient population after adjustment for available potential confounders.

2. Patients and methods

2.1. Patients

We collected individual data of patients included in one of four first-line chemotherapy randomised trials we coordinated: the FFCD-9601 trial [22], the FFCD-2000-05 Phase III trial,[24] the Actions Concertées dans les cancers COloRectaux et Digestifs (ACCORD) 13 trial [25] and the ML-16987 trial [26]. Trial characteristics are given in Table 1. All these trials recruited CRC patients with unresectable metastases defined as the inability to perform a R0 liver resection leaving a large enough liver remnant volume (>30% of the normal liver volume) or the presence of non-resectable metastatic sites (brain, bone, distant nodes, etc.) and World Health Organisation (WHO) performance status (PS) lower or equal to 2. All decisions regarding treatment were made by a multidisciplinary board including surgeon, radiologist and oncologist. Patients who had undergone a resection of the primary tumour prior to trial entry formed the resection group, while the others formed the non-resection group. As in all these trials a history of previous palliative chemotherapy was an exclusion criterion, all resections took place before starting first-line chemotherapy.

Patients were eligible for the present study if they had CRC and synchronous metastases, defined as metastases diagnosed less than 100 days after CRC diagnosis. Patients who underwent resection of their primary

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