**Epidemiology and Natural History**

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**Abstract** Although the vast majority of patients with a large-bowel primary have tumors amenable to curative resection at the time of diagnosis, the disease recurs in more than half of the patients, with the liver involved in up to two-thirds of the cases. Synchronous liver metastases are diagnosed in approximately 15% of the cases. In such patients, liver disease represents the sole site of distant metastases in more than 75%. Metachronous liver metastases develop in 16–20% of patients usually within the first 3 years. Untreated liver metastases have a grim prognosis. Liver resection is the only potentially curative treatment although only 20% of patients can be considered as candidates for surgery.

**1.1 Introduction**

Colorectal cancer is the fourth most common neoplasm worldwide, with approximately 1.2 million new cases diagnosed each year [1]. Significant international variations in the number of incident cases have been observed, with the highest rates reported in Europe, North America, and Oceania [2].

In Italy, based on data from the Italian Network of Cancer Registries (AIRTUM), which collects epidemiologic information from both general and specialized population-based cancer registries covering more than 32% of the entire Italian resident population (approximately 19,000,000 people), it has been estimated that in 2010 more than 29,200 new cases of colorectal cancers will be diagnosed among men and more than 17,500 among women. These crude numbers correspond to a cumulative risk (0–74 years) of developing a colon cancer of about 34.3‰ in men (i.e., 1 case every 29 men) and 22.2‰ in women (i.e., 1 case every 45 women) [3]. Mortality trend analyses for selected countries across the globe reporting highly accurate long-term mortality data have demonstrated that, in the period 1995–2005, colorectal cancer mortality significantly decreased in both males and females in longstanding, economically developed nations such as the United States, Australia, and the majority

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of Western Europe. Nonetheless, colorectal cancer still represents the second leading cause of cancer-related deaths. In fact, even though 85% of patients with a large-bowel primary have tumors amenable to curative resection at the time of diagnosis, the disease recurs in more than half of the patients, with the liver involved in up to two-thirds of the cases.

In most of the surgical literature on colorectal liver metastases, concise epidemiologic information on the incidence of synchronous and metachronous hepatic metastases and on resectability rates are provided, usually with reference to hospital-based reports. However, these data are limited by recruitment bias, since they are extrapolated from series of patients referred to tertiary care centers. Therefore, these incidence rates cannot be regarded as reference values for the entire population. Rather, population-based studies are essential for providing non-biased, truly representative data on the incidence, management, and prognosis of hepatic synchronous and metachronous metastases. Yet, such studies are rare because of the inherent problems in data collection from the entire population of patients with large-bowel cancer within a particular area. In the following, epidemiologic data will be discussed based on the few available studies conducted at a population level [4-6].

1.2 Epidemiology

The incidence of synchronous metastases has been reported to vary widely, between 15 and 30%. Using a population-based cancer registry, Manfredi et al. [4] recently analyzed 13,463 patients diagnosed with a large-bowel cancer over a 25-year period (1976–2000) in two administrative French areas, the Côte-d’Or and the Saône-et-Loire, with a resident population of more than 1 million people. The incidence of individuals with synchronous liver metastases identified during the diagnostic workup or in the course of treatment was 14.5%. Similar data have been reported in previous studies from Western Europe [7], France [8], and Australia [9]. In approximately 77% of the cases, Manfredi et al. [4] found that liver metastases were the sole distant secondary tumor, while in 23% of the cases they were associated with other visceral metastases. Synchronous liver metastases were more frequent in males (15.9%) than in females (12.8%), with age-standardized incidence rates of 7.6 and 3.7 per 100,000, respectively (sex ratio 2.1). Interestingly, the incidence of synchronous liver metastases was significantly influenced by the age at diagnosis: 19.8% before age 55, 16.7% between 55 and 64, 16.0% between 65 and 74, and 11.7% in patients 75 and over. Conversely, no correlation was demonstrated with the site of the primary tumor: 14.8% for colon cancers and 13.9% for rectal cancer. Compared to patients who developed secondary liver tumors after the treatment of their primary tumor, patients with synchronous metastases exhibited a higher number of liver deposits and a more frequent bilobar distribution. Rather disappointingly, analysis of temporal trends showed that the incidence of synchronous liver metastases was relatively stable over time. This is probably attributable to advances in preoperative