Abstract. Liver and pulmonary metastases (PMs) are relatively common in patients with colorectal cancer. The majority of metastases are suitable for surgical resection, and the effectiveness of metastasectomy is usually assessed based on overall survival (OS). Metastasectomy provides a mean 5-year OS rate of approximately 50%, but the results are better in patients with liver metastases compared to those with PMs. Unfortunately, the presence of bilateral or multiple PMs represents a relative contraindication to surgical metastasectomy. Unresectable PMs can be safely treated with percutaneous radiofrequency ablation or radiotherapy, but the reported results vary widely. Several clinical prognostic factors affecting OS after metastasectomy have been reported, such as number of PMs, hilar or mediastinal lymph node involvement, disease-free interval, age and gender, resection margins, size of the metastases, neoadjuvant chemotherapy administration, and histological type of the primary cancer. The accurate evaluation of all clinical prognostic factors, circulating and immuno-histochemical markers, and the study of gene mutational status will lead to a more accurate selection of patients scheduled to metastasectomy, with the aim of improving outcome.

Colorectal cancer (CRC) is a common malignancy, with approximately 1,360,000 new cases each year worldwide (1). However, in the USA, an annual decline in CRC incidence rate of 3.6% has been observed during the past five years (2). The postoperative overall survival (OS) of patients varies widely, ranging between 90% and 10%, according to the stage of the disease at the time of surgery (3). In the European Union, the estimated death rates per 100,000 people for the year 2015 were 10.19% and 9.36% in men and women, respectively (4). Preoperative staging of CRC requires both endoscopic and radiographic studies. In the primary diagnosis of CRC and early detection of cancer, colonoscopy is the best diagnostic tool. In selected patients, not scheduled for colonoscopy, contrast-enhanced multidetector computed tomography (CT) colonography (virtual colonoscopy) is considered a validated diagnostic modality, having a high accuracy in the definition of T and M, but little sensitivity and specificity in the definition of N (5, 6).

Metastases from Colorectal Cancer

In patients with CRC, liver metastases (LMs) and pulmonary metastases (PMs) are common, and approximately 20% of patients present with stage IV disease at the time of diagnosis (7). In the presence of either LMs or PMs from CRC surgical metastasectomy still represents the treatment of choice, prolonging OS and providing several long-term benefits (8, 9). The data obtained from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) registry show that the majority (67.4%) of patients with stage IV CRC underwent primary tumor resection, and that the overall postoperative survival rate increased progressively over the two past decades (10). However, especially in patients with multiple or surgically difficult-to-remove metastases, other therapeutic options should be considered, such as cytotoxic chemotherapy and targeted...
therapies (11), external radiotherapy (12, 13) and radiofrequency ablation (14-16). It has been reported that 5-6% of colon cancers and 10-18% of rectal cancers spread to the lung, with an overall incidence of PMs up to 15% (17). Another review study found that the incidence of isolated PMs was 6% and 12%, respectively, and that isolated PMs were uncommon (18). According to the Danish Colorectal Cancer Group (DCCG) database, the occurrence of a synchronous PM in patients with CRC accounts for 7.5%, and approximately one third are exclusively localized in the lung (19). The National Institute of Clinical Excellence (NICE) recommends the use of CT scanning of both the thorax and upper and lower abdomen for staging CRC (20). Unfortunately, CRC patients usually have a relatively advanced age, and thus pulmonary nodules are very common findings, ranging from 4% to 42% of all chest CT performed (21). However, the risk that one of these nodules can be a metastasis is less than 30%, and some studies suggest selecting patients at risk of LMs, such as those with lymph node involvement and LMs, before performing CT study (17, 21). According to a recent meta-analysis, contrast-enhanced magnetic resonance imaging (MRI) is the imaging study of choice in evaluating LMs, especially after neoadjuvant chemotherapy, and 18F-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG PET) should be considered a second-line imaging modality (22, 23). Kim et al. (24) reviewed 319 patients (median age=60 years, range=26-89 years) with CRC and no LMs, and found that 136 (42.6%) had indeterminate lung nodules on CT, out of which 14.7% were PMs. A prospective analysis study found that 8.5% and 4.3% had PMs or other pulmonary malignancies, respectively, suggesting to use chest CT as screening imaging study, followed by 18F-FDG PET combined with perfusion CT (PET/CT) in the presence of pulmonary nodules revealed on CT (25). Other imaging studies for staging patients with CRC are available, including dynamic enhanced MRI and diffusion-weighted MRI, but they are not routinely used (26).

Treatment of Pulmonary Metastases

The optimal treatment strategy of pulmonary metastasectomy (PMx) requires a careful definition of patients with potentially resectable PMs, according to both clinical and non-clinical parameters. The feasibility and usefulness of PMx was described for the first time in the 1940s (27, 28). Since then, a number of studies have reported on the advantages of surgery in patients with PMs of different origin. Currently, PMx is routinely performed worldwide, representing an effective option strategy in patients with metastatic CRC, but the short- and long-term results vary widely. The criteria used in selecting patients and the multimodal adjuvant treatment administered may justify the different OS rates reported by the authors (19, 29). In some studies, patients who underwent simultaneous PMx and liver metastasectomy had similar or slightly reduced OS compared to those with exclusively PMs, and the number of metastases represented an independent factor affecting survival (30-32). Adjuvant chemotherapy usually improves the disease-free interval (DFI) after surgery (33). Patients with PMs as first site of metastasis have a worse outcome, while re-metastasectomy may lead to OS rates up to 70%, justifying an aggressive surgical approach (34, 35). However, other studies report that the 5-year OS after repeated PMx ranges from 32% to 42% (36, 37). Unfortunately, patients with previously resected LMs and multiple PMs, have shorter DFI and OS (35-38).

CT-guided radiofrequency ablation causes coagulation necrosis of the metastatic tissue and is usually suggested in selected patients with multiple and surgically difficult-to-treat PMs. The results are promising, and the estimated 3- and 5-year OS range between 44-65% and 20-51%, respectively, but the 3-year tumor-free survival is approximately 15% (14, 15). Radiotherapy for isolated PMs, using different radiation techniques, can be effective in patients unsuitable for surgery, achieving 3-year OS rates ranging from 40% to 60%, but a 5-year overall relapse-free survival less than 20% (12, 13).

Prognostic Factors Affecting Outcome

Several clinical prognostic factors (PFs), including serum tumor markers, affecting outcome have been described. We analyzed the results of 15 studies involving a total of 1,669 patients (median=89, range=51-229 patients per study) that met the following criteria: (i) at least 50 patients with PMs from CRC surgically resected with curative intent; (ii) 5-year OS reported in the study; (iii) both univariate and multivariate analysis of PFs of survival presented. The mean 5-year OS was 49% (median 45%, range 25-72%) (Figure 1). No correlation was found (R=0.20, p=0.48) between number of patients and OS rate, and thus the surgical experience does not seem to affect outcome.

Table I resumes the PFs reported in the studies selected for our analysis (8, 9, 29, 39-50). The main independent predictors of worse results were elevated preoperative serum levels of carcinoembryonic antigen (CEA), the presence of multiple or bilateral PMs vs. single or unilateral PMs, hilar or mediastinal lymph node involvement, and a shorter DFI from PMx (Figure 2). Negative PFs were also no neoadjuvant chemotherapy administration (9, 47), younger (<60) or older (>60) age (43, 8), and incomplete (R1) vs. complete (R0) pulmonary resection (9, 49). Other negative PFs were male gender, size of the PMs, shorter interval for development of PMs from CRC resection, and histological type other than well-differentiated adenocarcinoma (8, 43, 45, 46). Many
serum tumor markers other than CEA, such as carbohydrate antigen (CA) 19-9 and tissue polypeptide-specific antigen (TPS), alone or in combination have been reported to be useful in predicting the onset of metastases and results of PMx (48, 51, 52). Simultaneous multi-analyte assay of a panel of circulating markers, including CEA, CA 19-9, CA 72-4, cytokeratin fragment (CYFRA) 21-1 and osteopontin, can be used for CRC screening, but not for revealing metastases, while baseline preoperative C-reactive protein measurement inversely correlates with OS, regardless of the presence of PMs (53, 55). In addition, several immunohistochemical markers, including the overexpression of FBJ murine osteosarcoma viral oncogene homolog B (FOS-B), tumor-suppressor protein p53, cellular proliferation protein Ki-67 and stromal expression of heat-shock protein 27 (Hsp27) may correlate to survival of patients with metastasized CRC (56-59). In certain studies, the intratumoral expression of thymidylate (TS), orotate phosphoribosyltransferase (OPRT) and dihydropyrimidine dehydrogenase (DPD) are closely related with efficacy of chemotherapy (60).
More recently, molecular markers and oncogene mutations have been found to be related to PMs development, also affecting the results of PMx. Kristen rat sarcoma viral oncogene homologue (KRAS) is an essential component of the epidermal growth factor receptor (EGFR) signaling cascade, and KRAS gene mutations promote tumor cells invasion and are usually associated with a poor prognosis (58, 61). KRAS and v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutations were found to be independent PFs for CRC LMs, and can be useful in selecting patients requiring metastasectomy (62). In patients with CRC, these mutations are associated with high incidence of PMs and reduced OS after PMx (62-65). The VICTOR (Vioxx® in Colorectal Therapy: Definition of Optimal Regime) trial evaluated 859 CRCs, detected oncogene mutations in 4 of 19 oncogenes, including KRAS, BRAF, the phosphatidylinositol 3-kinase pathway member PIK3CA and the neuroblastoma RAS viral oncogene homologue (NRAS), and found a strong relationship between KRAS mutation and PMs (66). In some studies, the resistance to EGFR inhibitors, including gefitinib and lapatinib, was associated with RAS and BRAF mutations (67).

Conclusion

The majority of PMs are suitable for surgical resection and the effectiveness of PMx is usually assessed based on OS rates, because other validated selection criteria are not reliable (68). In certain studies, the site of primitive tumor (colorectal vs. non-colorectal) and the presence of simultaneous LMs does not significantly affect the results of PMx, which are similar to those obtained in patients with PMs exclusively (30, 32, 69). Unresectable PMs can be safely treated with percutaneous radiofrequency ablation or radiotherapy, with palliative intent, but the result varies widely (12, 13, 15, 16, 70, 71). A careful evaluation of all clinical PFs, circulating immunohistochemical and molecular markers, and the gene mutational status will lead to a more accurate selection of patients scheduled for metastasectomy, with the aim of improving DFI and OS.

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