



Surgical treatment of pulmonary metastasis in colorectal cancer patients: Current practice and results



Matthieu Zellweger¹, Etienne Abdelnour-Berchtold¹, Thorsten Krueger¹, Hans-Beat Ris¹, Jean Yannis Perentes¹, Michel Gonzalez^{1,*}

Division of Thoracic Surgery, Centre Hospitalier Vaudois (CHUV), Lausanne, Switzerland

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ABSTRACT

Colorectal cancer (CRC) is a frequently occurring disease, yet diagnosed at a local stage in only 40% of cases. Lung metastases (LM) appear in 5–15% of patients and, left untreated, carry a very poor prognosis. Some CRC patients may benefit from a potentially curative LM resection, but success and benefit are difficult to predict. We discuss prognostic factors of survival after lung metastasectomy in CRC patients under several scenarios (with/without prior liver metastases; repetitive pulmonary resections).

We reviewed all studies (2005–2015) about pulmonary metastases surgical management with curative intent in CRC patients, with a minimum threshold on the number of patients reported (without prior liver metastases: $n \geq 100$; with prior resection of liver metastases: $n \geq 50$; repetitive thoracic surgery: $n \geq 30$).

The picture of the prognostic factors of survival is nuanced: surgical management demonstrates clear successes and steady progress, yet there is no single success criterion; stratification of patients and selection bias impact the conclusions. Surgical management of liver and lung metastases may prolong life or cure CRC patients, provided the lesions are fully resected and patients carefully selected. Repeat lung metastasectomy is a safe approach to treat patients in selected cases.

In conclusion, there is no standard for surgical management in CRC patients with pulmonary metastases. Patients with isolated unilateral lung metastasis with normal CEA level and no lymph node involvement benefit the most from surgery. Most series report good results in highly selected patients, but instances of long-term disease-free survival remain exceptional.

1. Introduction

Colorectal cancer (CRC) is one of the four major cancer sites, along with breast, lung and prostate (Siegel et al., 2013; Siegel et al., 2014a). It is estimated that approximately 1 in 20 people will develop CRC over their lifetime, although this number may be decreasing, indicating progress in CRC detection or prevention (Siegel et al., 2017; Siegel et al., 2014b). Approximately 65% of all patients developing CRC will survive 5 years after the diagnosis (Siegel et al., 2013; Siegel et al., 2014b), but this figure varies widely with the CRC stage at detection (Siegel et al., 2013; Siegel et al., 2014a). Overall, CRC is still the third most common cancer and the third leading cause of cancer death in men and women in the United States (Siegel et al., 2014b).

It is estimated that only 40% of patients with CRC are diagnosed when the disease is still localized (Siegel et al., 2014b). The rest of the patients present a disease, which is either regional or distant, with liver

metastases as the most frequent (and sometimes the only) distant manifestation (Simmonds et al., 2006; Weiss et al., 1986; Hugh et al., 1997), and lung metastases (LM) in 5–15% of CRC patients (Gonzalez et al., 2012). Left untreated, metastatic CRC carries a very poor prognosis with a 5-year survival rate of less than 5% (Stangl et al., 1994; Poon et al., 1989). During the last two decades, new chemotherapeutic agents have been developed, such as irinotecan, oxaliplatin and monoclonal antibodies against EGFR and VEGF. These allow prolonged progression-free survival and overall survival in metastatic colorectal cancer (Douillard et al., 2000; Saltz et al., 2000; Goldberg et al., 2004; Van Cutsem and Geboes, 2007; Van Cutsem et al., 2009). In addition, surgery and anesthesia progresses have made it possible to offer aggressive surgical resection with complete resection of different metastatic site and excellent survival rate up to 50% at 5 years in previously difficult cases such as for instance in case of hepatic metastases (Abdalla et al., 2004).

* Corresponding author at: Division of Thoracic Surgery, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland.

E-mail addresses: Matthieu.zellweger@epfl.ch (M. Zellweger), Etienne.Abdelnour@chuv.ch (E. Abdelnour-Berchtold), Thorsten.Krueger@chuv.ch (T. Krueger), Hans-Beat.Ris@chuv.ch (H.-B. Ris), Jean.Perentes@chuv.ch (J.Y. Perentes), michel.gonzalez@chuv.ch (M. Gonzalez).

¹ All authors have approved the final article.

The majority of patients with pulmonary metastases will undergo palliative disease management, including chemotherapeutic approaches, due to the frequent invasion of other organs. In addition, surgery can be proposed as palliation in selected patients, suffering either uncontrollable pain as a result of chest wall invasion, massive hemoptysis or retention pneumonia due to centrally located metastases.

Aside from the purely palliative surgical management, a sub-set of CRC patients may benefit from a potentially curative LM resection (Pfannschmidt et al., 2007), provided some strict criteria are met: all LM are technically resectable; patient can tolerate pulmonary resection; the primary CRC site is controlled; no extra-thoracic lesion is detectable (with the exception of resectable liver metastases) (National Comprehensive Cancer Network, 2009).

However, it is still unclear which patients will really benefit from this curative surgical management. Various prognosis factors have been reported (Gonzalez et al., 2012), aiming to facilitate the clinician's decision process. The difficult decision facing the clinician is compounded by the natural history of LM, which may take various courses: LM is synchronous with primary CRC; LM appears after a liver metastasis was managed; LM appears as the first distant manifestation of the primary CRC; LM appears after a previous lung metastasis was managed. These elements make it difficult to clearly ascertain the impact of surgery on the survival of the patients, leaving a question mark as to what is the best treatment course for patients with an LM from a primary CRC. Moreover, surgical approaches are now better accepted with the development of video-assisted thoracoscopic surgery (VATS) allowing a safe resection with lower morbidity.

Although PulmiCC trial (Treasure et al., 2011) is comparing best medical treatment with and without pulmonary surgical resection and investigating the real benefit of pulmonary metastasectomy, pulmonary metastasectomy remains an accepted procedure for physicians and patients in case of localized pulmonary metastases. Recently, novel non-surgical strategies (such as stereotaxic radiotherapy and radiological ablation by radiofrequency) are now investigated as an alternative to surgery, but remain outside the scope of this article.

Several retrospective studies have supported the role of pulmonary metastasectomy in different tumors types and particularly in colorectal cancer patients. Nonetheless, it is currently not possible to identify patients who may benefit mostly from this surgical strategy. Pfannschmidt et al performed a systematic review in 2007 about pulmonary metastasectomy in CRC patients (Pfannschmidt et al., 2007). The authors collected 20 surgical series published from 1995 to 2006 and including 1684 patients. The mortality rate was low (0–2.5%) and the 5-year survival was lower when incomplete resection (0–21%) in comparison with complete resection (24–56%). Several prognostic factors of poorer survival were identified such as multiple metastases, thoracic lymph node involvement or elevated pre-thoracotomy CEA level. However, there was a great discrepancy in term of results due to the fact that most of these factors were not found as relevant in most studies or not even analyzed. The systematic review was updated in 2011 (Pfannschmidt et al., 2010) on behalf of the ESTS working group for pulmonary metastasectomy and included 11 studies and 1307 patients with a 5-year survival rate ranging from 40 to 68% with the same conclusion on prognostic factors of survival than the previous review. We performed a meta-analysis including twenty-five surgical studies series from 2000 to 2011 with a total of 2925 patients to analyze preferentially the outcome of patients treated with modern surgical, anesthetic and radiological techniques (Gonzalez et al., 2013). Four parameters were associated with poor survival: (1) a short disease-free interval between primary tumor resection and development of LM (HR 1.59, 95% confidence interval [CI] 1.27–1.98); (2) multiple LM (HR 2.04, 95% CI 1.72–2.41); (3) positive hilar and/or mediastinal lymph nodes (HR 1.65, 95% CI 1.35–2.02); and (4) elevated prethoracotomy carcinoembryonic antigen. In parallel, Salah et al published in 2013 (Salah et al., 2013) a pooled analysis of individual data of patient of 8 previously published studies with 927 patients with an overall 5-year-

survival rate of 54%. They could identify 3 prognostic factors of poorer survival on multivariate analysis: CEA level of more than 5, more than 2 metastases and DFI of more than 36 months. They could propose a simple clinical model and stratify the risk of survival at 5-year depending on the number of risk factors.

The aim of this present review is to refine our previous conclusions in light of more recent developments in this field. We aim to discuss the prognostic factors of survival after lung metastasectomy in CRC patients with or without prior liver metastases and in CRC patients undergoing repetitive resection for pulmonary metastases.

2. Methodology

We reviewed all studies published between 2005 and 2015, which report results of pulmonary metastases management with curative intent in CRC patients by surgical approach. The restriction to studies published between 2005 and 2015 ensures that only results pertaining to modern surgical techniques are reported. We further restricted our analysis to studies reporting results on a minimum number of patients: $n \geq 100$ in case of CRC patients with LM and without prior liver metastases; $n \geq 50$ in case of CRC patients with LM and with prior resection of liver metastases; $n \geq 30$ in case of CRC patients with LM who underwent repetitive thoracic surgery. This allows us to derive some statistical power from work reported by centers with continuing experience in the management of CRC patients.

Relevant studies were identified by searching MedLine. The following search terms were used: lung metastases, pulmonary metastases, lung metastasectomy, colon, colorectal cancer, surgery. The research was restricted to publications in English. Two investigators performed the literature research independently (MG and MZ). Relevant articles referenced in the publications were also searched for additional studies for potential inclusion. The “related article” function was used to widen the search criteria. Articles excluded at the first selection included teaching and review articles, technical reports and those containing no relevant data concerning the treatment approaches selected. When a study had generated multiple publications, the most recent study was used to extract data.

We extracted various elements from the studies: number of patients; mean age; number of lung metastases treated; type of disease (uni- or bilateral); median survival; 5-year survival; prognostic factors of prolonged survival; number of liver metastases; 5-year disease-free survival after initial or repeat pulmonary resection. It should be noted that due to the varying designs of the studies considered, not all elements are present in all studies. In a separate table (Table 2), we also reported, if available, the statistical measures (HR: Hazard Ratio; IH: Increased Hazard; OR: Odds Ratio; RR: Relative Risk) of five risk factors correlated with overall survival, which we identified as relevant in a previous study (Gonzalez et al., 2013).

3. Surgical results of lung metastasectomy

3.1. Surgery for LM

Twenty-one series including more than 100 patients have been published between 2005 and 2015 (Table 1) (Yedibela et al., 2006; Welter et al., 2007a; Onaitis et al., 2009; Watanabe et al., 2009; Riquet et al., 2010; Hwang et al., 2010; Borasio et al., 2011; Hamaji et al., 2012; Blackmon et al., 2012; Kim et al., 2012; Nozawa et al., 2012; Younes et al., 2013; Iida et al., 2013; Embún et al., 2013; Renaud et al., 2014; Bölükbas et al., 2014; Cho et al., 2014; Zampino et al., 2014; Meimarakis et al., 2014; Hunt et al., 2015; Cho et al., 2015). Overall, these series represent a total of 8361 patients who underwent thoracic surgery with a curative intent. Five-year survival rates after the first pulmonary metastasectomy ranged from 24 to 82%, while median survival ranged from 35 to 70 months.

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