Clinical Oncology xxx (2016) 1–8

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Exploratory Analysis on Overall Survival after Either Surgery or Stereotactic Radiotherapy for Lung Oligometastases from Colorectal Cancer

A.R. Filippi *, F. Guerrera †, S. Badellino *, M. Ceccarelli ‡, A. Castiglione ‡, A. Guarneri *, R. Spadi §, P. Racca §, G. Ciccone ‡, U. Ricardi *, E. Ruffini †

* *Department of Oncology, Radiation Oncology, University of Torino, Italy*
† *Department of Surgical Sciences, Thoracic Surgery, University of Torino, Italy*
‡ *Unit of Clinical Epidemiology, Città della Salute e della Scienza and CPO Piemonte, Torino, Italy*
§ *Medical Oncology, Colorectal Cancer Unit, Città della Salute e della Scienza, Torino, Italy*

Received 13 May 2015; received in revised form 13 January 2016; accepted 14 January 2016

Abstract

Aims: Lung metastasectomy and, more recently, stereotactic body radiotherapy (SBRT), are frequently proposed to stage IV oligometastatic colorectal cancer (CRC) patients. In the absence of a randomised comparison between the two treatments, we aimed to retrospectively explore the effect on overall survival and progression-free survival (PFS) in a comparative cohort study.

Materials and methods: We included patients who consecutively underwent surgery ($n = 142$) or SBRT ($n = 28$) as first local therapy at the time of lung progression, between 2005 and 2012. Both overall survival and PFS functions according to treatment were calculated using the Kaplan–Meier method and compared using the Log-rank test. The effect of treatment on overall survival and PFS was estimated by Cox models using different adjustment methods.

Results: Patients receiving SBRT were older and were treated more recently, whereas the two cohorts were similar for most baseline prognostic factors. Overall survival at 1 and 2 years was 0.89 and 0.77 for SBRT and 0.96 and 0.82 for surgery ($P = 0.134$), respectively. Multivariable analyses did not highlight a clear treatment effect on overall survival (adjusted hazard ratio$_{\text{SBRT versus surgery}} = 1.71$; 95% confidence interval 0.82–3.54; $P = 0.149$) and even smaller differences using the inverse probability treatment weighting method (hazard ratio$_{\text{SBRT versus surgery}} = 1.28$, 95% confidence interval 0.58–2.82; $P = 0.547$). The results of PFS were unreliable because different follow-up protocols were applied in the two cohorts.

Conclusion: With limitations consisting in the retrospective observational design and different sample sizes, the results of this explorative analysis indicate that overall survival probability after SBRT is similar to surgery for the first 2 years from treatment. This finding supports the need for high-quality trials comparing different treatment modalities for lung oligometastases from CRC.

Key words: Colorectal cancer; lung metastasectomy; lung metastases; stereotactic ablative radiotherapy; stereotactic body radiotherapy

Introduction

Aggressive metastasis-directed local treatments, with or without systemic therapy, are frequently proposed to oligometastatic colorectal cancer (CRC) patients, especially for liver and lung localisations [1]. Determining the advantages or the possible superiority of this approach in comparison with systemic therapy alone or observation is challenging because of the predominantly retrospective nature of existing data, which have raised substantial concerns for selection biases (performance status, disease-free interval, small metastatic burden). The best evidence for the potential advantage of local therapies for oligometastatic disease comes from surgery for lung or liver metastases [2], and lung metastasectomy may be considered a standard option for oligometastatic CRC patients, due to the large amount of retrospective data and few prospective studies [3]. Among local treatments, stereotactic body radiotherapy (SBRT) is increasingly proposed for its very favourable toxicity profile [4,5]. However, survival results after SBRT are retrospective

Author for correspondence: A.R. Filippi, Department of Oncology, University of Torino, Via Genova 3, 10126 Torino, Italy. Tel: +39-011-6705352.
E-mail address: andreariccardo.filippi@unito.it (A.R. Filippi).

http://dx.doi.org/10.1016/j.clon.2016.02.001
0936-6555/

and widely variable, reflecting the intrinsic heterogeneity of the analysed cohorts (different primary histology, disease natural histories, systemic treatments, follow-up protocols and other confounding factors) [6–9]. A few studies have specifically addressed the role of SBRT in patients affected by lung metastases from CRC, with promising results [10–13]. These findings raised the interest on a carefully adjusted comparison between SBRT and lung resection, as the reported 2 year overall survival after surgery is notable, in the range 64–88% [3,14]. Ideally, as for any treatment, SBRT should be compared with surgery and/or observation in a prospective randomised trial, but there are some difficulties in the design, enrolment and conduction of such a study, for a variety of reasons [15]. The first aim of this retrospective study was to carry out an adjusted comparison of the efficacy, in terms of overall survival, of SBRT versus surgery for patients affected by CRC lung oligometastases. Moreover, as a secondary analysis, we aimed to explore and to evaluate the effect of treatment on progression-free survival (PFS).

Materials and Methods

Patient Population

In this single-institution study we included all patients treated at the time of their first diagnosis of lung metastases with either surgery or SBRT in the time interval 2005–2012 (surgery = 142, SBRT = 28). All patients satisfied the following pre-treatment clinical criteria: (i) histological diagnosis of primary colorectal adenocarcinoma previously treated with radical surgery; (ii) number of lung metastases ≤ 5; (iii) maximum tumour diameter ≤ 50 mm; (iv) adequate pulmonary function (forced expiratory volume in the first second (FEV_1) > 40% predicted and diffusion capacity of the lung for carbon monoxide (DLCO) > 40% predicted); (v) Eastern Cooperative Oncology Group (ECOG) performance status 0–1; (vi) controlled primary tumour (no evidence of recurrent disease in the abdomen) and/or controlled extra-lung metastases (metastases successfully controlled by local therapies and/or previous systemic therapies).

Lung metastases were defined as the new appearance of nodules ≥ 8 mm in the lung parenchyma. SBRT or surgery was proposed to patients at the discretion of the treating physician, often after discussion within a multidisciplinary team, without applying any specific selection criteria for surgery or SBRT.

The study was approved by our Institutional Review Board.

Surgery

The ideal surgical approach was chosen according to the number, the location and the laterality of the lesions: usually, muscle-sparing axillary thoracotomy was the access of choice. In case of synchronous bilateral lesions, the surgical timing was personalised on each patient characteristic. Complete palpation of the lung was carried out in all cases, except in the case of thoracoscopic procedures. Wedge resection was accomplished in the case of peripherally located pulmonary nodules; anatomical resections (segmentectomy or lobectomy) were carried out in the case of multiple nodules in the same pulmonary segment or lobe, of large lesions or in the case of metastases deeply located in the pulmonary parenchyma. Lymph node assessment included hilar and mediastinal node sampling.

Stereotactic Body Radiotherapy

Lung metastases were either treated with three-dimensional conformal radiation therapy (3D-CRT) 2005–2010) or, more recently, with image-guided volumetric modulated arc therapy (IG-VMAT; 2010–2012). The technical details of both techniques have been previously described [9]. Briefly, for 3D-CRT each patient was immobilised in the supine position with a stereotactic body frame (SBF-ELEKTA® Oncology Systems), with a diaphragm compression device to reduce tumour motion. The target was outlined in sequential axial computed tomography images and the gross tumour volume contoured using a computed tomography lung window setting (1600–400 Hounsfield Units). The clinical target volume corresponded to the gross tumour volume. The planning target volume was generated adding a 5 mm margin in the axial plane and a 10 mm margin in the longitudinal direction, in order to compensate for set-up errors and organ motion. SBRT was delivered with an Elekta Precise™ linear accelerator (Elekta, Stockholm, Sweden), using six to eight static non-opposing, non-coplanar shaped fields, with 6–10 MV photons. For IG-VMAT, a frameless Bluebag® vacuum-pillow was used as the immobilisation device, and an internal target volume was defined in which the gross tumour volume included the tumour position in all phases of the normal respiratory cycle, outlined using a computed tomography windows setting. The internal target volume was expanded by 3 mm to create the planning target volume. Monaco™ software was used for treatment planning and the Monte Carlo algorithm for dose calculation. Treatments were delivered with an Elekta Axesse™ linear accelerator, with 6–10 MV photons and cone-beam computed tomography image guidance (for each treatment session). VMAT was planned with a single 360° arc. Dose limits to organs at risk were as follows: ipsilateral mean lung dose < 15 Gy_2 (radiation pneumonitis, $\alpha/\beta = 3.5$ Gy), spinal cord < 36 Gy_2 ($\alpha/\beta = 2$ Gy), skin < 56 Gy_2 (necrosis, $\alpha/\beta = 2.5$ Gy), trachea/main bronchi < 78 Gy_2 (stenosis/fistula, $\alpha/\beta = 3$ Gy), heart < 70 Gy_2 (pericarditis, $\alpha/\beta = 4$ Gy). Dose prescription was at the 80% isodose, and the dose-fractionation schedule was chosen by the treating radiation oncologist according to tumour size, location and organ at risk dose constraints.

Follow-up

Vital status, updated to March 2014, was obtained from the Piedmont Health Service Register, an administrative database including all the population covered by the Regional Health Service. According to clinical practice,

Please cite this article in press as: Filippi AR, et al., Exploratory Analysis on Overall Survival after Either Surgery or Stereotactic Radiotherapy for Lung Oligometastases from Colorectal Cancer, Clinical Oncology (2016), http://dx.doi.org/10.1016/j.clon.2016.02.001