

## Editorial

# Resection of the Primary Tumor in Asymptomatic or Minimally Symptomatic Patients with Stage IV Colorectal Cancer and Unresectable Metastases

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Colorectal cancer is a commonly diagnosed cancer. More than 25% of the patients have an initial diagnosis at a Stage IV, with a 5 year overall relative survival of 10-18% [1-3]. Simultaneous resection of the primary tumor and of all metastases can be conceptually curative; however, more than 80% of the patients presents with unresectable colorectal metastases. Primary tumor resection is an accepted therapeutic option in patients with major symptoms related to a Stage IV colorectal cancer, with unresectable metastases. Controversies exist about the opportunity of primary tumor resection in patients with no symptoms or mild symptoms. The basic philosophy for resection is that about 20% of the patients initially asymptomatic will develop major symptoms (obstruction, bleeding, perforation), requiring emergency surgery.

New chemotherapeutic agents have been introduced into clinical practice, including oxalplatin, bevacizumab, capecitabine, regorafenib. These new drugs, alone or in combination with fluorouracil and leucovorin, have been shown to prolong survival and to reduce the advent of major complications in patients with Stage IV colorectal cancer and unresectable metastases [4-8]. In the same period, endoscopic placement of self-expanding metallic stent has been slowly accepted in the clinical practice [3]. Complications after endoscopic stenting have been reduced with increasing experience, and stenting has been demonstrated to be a valid alternative in selected patients with Stage IV colorectal cancer and unresectable metastases [9-12]. Several retrospective studies have been reported. All studies show better results after primary resection of the tumor [13-18] reviewed the results of 26 studies which included 43,903 patients. Using random subgroup analysis, they tried to overcome the clinical and anatomic differences between subgroups. Patients receiving primary tumor resection plus chemotherapy/radiotherapy had longer overall survival. In 3 studies, details about Progression Free Survival were described. Random

subgroup analysis showed longer Progression Free Survival in patients who had primary tumor resection.

All the reported retrospective studies conclude that there is the possibility of significant selection bias, therefore caution should be used in analyzing results [19] tried to overcome the possibility of selection biases, using a propensity matching score. They analyzed the data of 10,371 patients with Stage IV colorectal cancer and unresectable metastases from the Netherlands Cancer Registry (2008-2011): 2,746 patients who had primary tumor resection. Using propensity matching score they found that patients who had primary tumor resection had a median survival of 17,2 months, while those who did not have surgery had a median survival of 11.5 months. In Cox regression analysis, primary tumor resection was associated with longer survival. In this study several important data were not reported, including T and histology of the primary tumor [20] using the same type of statistical analysis, did not find any influence of primary tumor resection in patients with stage IV colorectal cancer and unresectable metastases. There are also many conceptual differences between patients, in the way they could respond to targeted therapy [21-24] (Figure 1-3).

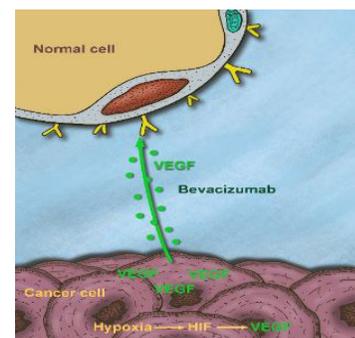
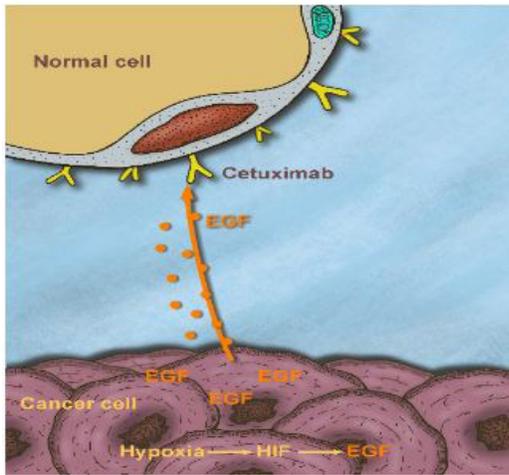
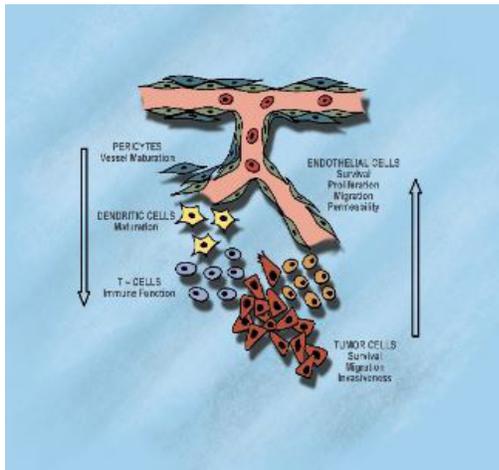


Figure 1: Schematic Drawing Representing the Inhibitory Action of Bevacizumab on VEGF.



**Figure 2:** Schematic Drawing Representing the Inhibitory Action of Cetuximab on EGF.



**Figure 3:** Schematic Representation of The Action of VEGF And EGF In Promoting Cancer Cell Growth and Diffusion.

The resection of the primary tumor has several theoretical advantages.

- Cells of the primary tumor produce high quantities of VEGF and EGF, which also can be found in the blood circulation [25]. These growth factors could have a stimulatory action on the liver metastases. Primary tumor resection eliminates the source of a potential continuous growth stimulus for liver metastases.
- The high levels of growth factors in the primary tumor could neutralize the majority of the targeted therapy, which will result unable to act on liver metastases
- Liver metastases, can differentiate from the primary tumor, with higher possibility of being sensitive to the biological drugs.

To these theoretical advantages, we should add the negative effect on the immunological system of surgery per se. Several multicenter prospective trials are being conducted in Germany, Korea and Spain, to analyze the importance of resection in these groups of patients. These studies probably will help to clarify some of the questions about this matter [26]. Patients with Stage IV colorectal cancer and unresectable metastases represent a significant heterogeneous group of patients. In the absence of clear guidelines, the treatment should be based on clinical judgment. An easy surgical act in a relatively young patient in acceptable general conditions seems advisable. Many questions remain about the association of chemotherapy in this scenario and which type of chemotherapy. There is the possibility of an aggressive chemotherapeutic regimen in patients with good conditions, with inevitable reduced quality of life. All these considerations should be taken into account. A close collaboration among surgeons, oncologists is essential, considering each patient in his individuality with his own needs and expectations.

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