

RESECTABILITY OF INITIALLY UNRESECTABLE LIVER METASTASES FROM COLORECTAL CANCER SHOULD NOT BE THE PRIMARY END POINT OF CLINICAL TRIALS

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Systemic chemotherapy of advanced colorectal cancer (CRC) adds around 9% 5-year survival rate with modern chemotherapy. [1] Such an outcome is substantially better when surgical resection of liver metastases is performed on very well selected patients. The shrinkage of tumor with proper medical treatment has improved over time, more and more resections of liver metastases that were initially considered unresectable are being performed by specialized surgeons.

The paradigm "better responses -> more resections -> better efficacy"[2] is encouraging, to the point that resectability is considered a potential primary end point of clinical trials. We could see why such an end point is so attractive to patients and physicians, but at the same time so misleading and biased that it should not be used as the primary end point in clinical trials. What drives our therapeutic choices in clinical practice is not the median effect, or the hazard ratio for survival, or the progression-free survival (PFS) advantage with a certain treatment over another, rather it is an individual patient could be "an outlier," ie, he or she might derive a significant benefit from therapy. In this regard, the ability of newer combinations to enable surgical resection of metastatic lesions that were not initially resectable is very attractive.[3] Following radical surgery, even those patients with initially unresectable disease will have a 30% chance of long-term survival,[4] which is similar to that of patients who undergo primary resection.[5] Offering patients with metastatic colorectal cancer a chance of cure represents the main driving force of our clinical practice. However, given the high probability that disease will recur within a few months of major liver surgery, is resectability by itself a relevant enough outcome to pursue? "Resectability" indicates a state of *potential resection*, it does not imply that the patient has had the tumor completely removed, is alive, well, and free of disease. Thus, it is important to recognize that resectability is just the first stage of a sequential process consisting of the following successive steps:

Table 1 illustrates the lack of compelling data available from clinical trials on this issue; the reported outcomes, in fact, refer only to patients who successfully underwent resection with curative intent, not to all patients considered eligible for radical surgery after "conversion chemotherapy."

Table 1. Resection after preoperative chemotherapy in recent colorectal cancer trials. The percentage of resection is much lower in phase III trials because patients were not selected for liver-limited disease.

Author, year	Regimen	Pts. with initially unresectable disease	Median duration of preoperative CT	% Pts. with secondary surgery	% Pts. with R0 resection	Median RFS after R0 surgery
Alberts SR, J Clin Oncol 2005	FOLFOX	42 (liver-limited disease)	6 months	40%	33%	19 months
Masi G, ASCO 2008	FOLFOXIRI	135	6 months	36%	15%	NR
Quandt F, ASCO 2004	FOLFOXIRI	34 (liver-limited disease)	3 months	88%	37%	12 months
De La Camara J, ASCO 2004	FOLFOXIRI	22	NR	50%	45%	NR
Tabernero J, J Clin Oncol 2007	FOLFOX + cetuximab	43	7 months	23%	21%	NR
Tagliaferri G, Ann Oncol 2006	AIO trial arm + cetuximab	21	6 months	23%	19%	NR
Tagliaferri G, S. Carlos Symposium 2008	FOLFOX or FOLFIRI + cetuximab	111 (liver-limited disease)	4 months	42%	35% FOLFOX-ad 37%, FOLFIRI-ad 34%	NR
Van Cutsem E, ASCO 2009	FOLFIRI + cetuximab	599	Not defined	9%	4.3% (9.8% in the liver-limited population)	NR
Bokemeyer C, J Clin Oncol 2009	FOLFOX + cetuximab	170	6 months	NR	4.7%	NR
Delaunoit T, Ann Oncol 2005	II Lv FOLFOX or IROX	795	5.5 months	3.3%	3%	18 months

Abbreviations: FOLFOX = folinic acid/5-fluorouracil/oxaliplatin; FOLFOXIRI = folinic acid/5-fluorouracil/oxaliplatin/irinotecan; AIO = arbeitsgemeinschaft internistische onkologie; FOLFIRI = folinic acid/5-FU/irinotecan; FL = irinotecan/5-FU/leucovorin; IROX = irinotecan/oxaliplatin.

1. the patient undergoes surgery,
2. the surgeon attempts to resect the tumor (up to 20% of these procedures result in an aborted open-close operation due to the presence of peritoneal metastases),
3. the tumor is resected by the surgeon,
4. all tumor deposits are resected with adequate margins,
5. the pathologist confirms that an R0 resection was performed,
6. the patient fully recovers from the procedure.

In general, 10–20 of 100 patients with initially unresectable disease will be considered eligible for liver surgery following neoadjuvant treatment. Only half of these patients, however, will be alive, well, and disease free after surgery. And when all is said and done, how long might the disease-free state be expected to last after surgery? For example, in a trial by Alberts et al specifically designed to assess the activity of FOLFOX4 as first-line therapy for patients with liver-limited metastases from colorectal cancer, tumor shrinkage occurred in 60% of the initial 42 patients, and resection was attempted in 40%. Among those patients who underwent surgery, 33% had an R0 resection, but disease recurred in 40% of these patients within 12 months. This casts doubts on the real value of such an aggressive treatment plan including combination chemotherapy and major surgery.

Thus, resectability is gaining more and more popularity among investigators, based on very shaky scientific ground. Let's consider the intrinsic peculiarities of a study that would compare two treatments, pursuing resectability of initially unresectable liver metastases as its primary end point, and let's consider the challenges that such a study would present. There are two types of errors in clinical trials—random error and bias. Random error is due to the natural variability of biological and clinical phenomena; bias is due to a specific selection that clinical investigators may make. The purpose of a clinical protocol is to minimize these two types of errors. Accruing a large number of patients and randomizing them are the most effective means of minimizing variability (random error), whereas having strict eligibility and exclusion criteria and analyzing data on an *intention-to-treat* basis are key to minimizing bias. In the case of a trial evaluating neoadjuvant therapy of initially unresectable liver metastases, these basic concepts constitute prohibitive challenges.

Accruing a large number of patients eligible for such a study is very difficult due to the intrinsic complexity of any multimodality treatment trial. Yet, this problem can be overcome.

The key eligibility criterion for a trial like this is that the disease is unresectable at the time of study entry, but may become resectable if the lesions shrink sufficiently after treatment ment. There is nothing more variable than the evaluation of resectability.[7] Accessing difficult anatomic locations may be prohibitive for a general surgeon but still possible for an experienced liver surgeon. The definition of "resectable" is changing over time.[8] Initially focusing on "what comes out," it has progressively shifted toward "what's left in," with "resectable disease" considered that which can be removed while preserving adequate hepatic reserve. Thus, what constitutes "resectable" still remains highly subjective.

The temptation not to perform an intention-to-treat analysis is very strong in these complicated conditions, as best exemplified by the EORTC (European Organization for Research and Treatment of Cancer) trial[9] that has generated so much debate recently.[10] We can speculate that the real hallmark of benefit is neither response nor resectability nor the R0 resection rate, but rather how long the patient shows no evidence of disease after an R0 resection; to wit, recurrence-free survival (RFS). As a reference point, a 6-month RFS seems too short an interval when we engage in costly and risky programs of preoperative treatment followed by surgery. It is our feeling that the RFS should be at least 12 months in a significant proportion of patients. Anything below 25%–30% of patients living relapse-free for a minimum of 12 months would have little clinical relevance and would be too costly. This concept may apply both to clinical practice (where exceptions can obviously be made) and trial design. Our group is conducting a trial where clearly unresectable advanced colorectal cancer patients are treated with a combination of three biologics and a chemotherapy doublet, with the "ambitious" primary end point of 12-month RFS in at least 30% of enrolled patients. We certainly have set a very high bar for success. But in light of the costs and morbidities of this approach we need innovative end points that realistically merge clinical relevance with toxicity and cost. The chosen end point should minimize the bias connected with defining resectability and lead to a more careful selection of patients for maximum benefit.

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