Nonsurgical Approaches to Colorectal Cancer

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LEARNING OBJECTIVES
After completing this course, the reader will be able to:
1. Describe the potential for nonsurgical approaches to colon cancer.
2. Discuss radiofrequency ablation data for metastatic colon cancer.
3. Discuss the utility of radiation in metastatic colon cancer patients.

ABSTRACT
It is time to challenge the current orthodoxy that frowns upon surgical and nonsurgical methods of tumor reduction for patients with metastatic colon cancer. Although the studies conducted with radiofrequency ablation, chemoembolization, and radiation therapy in patients with metastatic colon cancer have tended to be small and may have been subject to selection bias, they have produced survival data that require careful consideration. At the very least, it is clear that locoregional approaches to debulking tumors are feasible and that their combination with systemic chemotherapy should be investigated.

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INTRODUCTION
The majority of clinicians concerned with the treatment of metastatic colorectal cancer (CRC) continue largely to dismiss the potential of organ-specific interventions such as radiofrequency ablation (RFA), chemoembolization, and radiation therapy. Perhaps now is an appropriate time for their reappraisal.

The primary purpose of any cancer treatment is to enable patients to feel better and live longer. The latter requires either that the tumor be prevented from growing or that there be a logarithmic reduction in tumor cells sufficient to have an impact on the natural history of an individual patient’s cancer [1, 2]. While the target of cytostasis is the subject of numerous preclinical and clinical studies (e.g., angiogenesis inhibitors), we currently have safe surgical and nonsurgical approaches to achieve tumor cytoreduction.

It is becoming increasingly evident that new chemotherapy in the management of colon cancer is likely achieving an impact on survival through cell kill. Hobday et al. demonstrated that long-term survival is rare among metastatic CRC patients treated with 5-fluorouracil (5-FU) [3]. Of 3,514 patients enrolled in North Central Cancer Treatment Group (NCCTG) studies over the period 1974–1993, 2,580 were treated with a 5-FU regimen. Only 43 patients (1.2%) corresponded: David P. Ryan, M.D., Medical Director, Tucker Gosnell Gastrointestinal Cancer Center, Massachusetts General Hospital Cancer Center, Boston, Massachusetts 02114, USA. Telephone: 617-726-8515; Fax: 617-643-1894; e-mail: dpryan@partners.org
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are known to have survived longer than 5 years. Thirty-six patients received only chemotherapy. Seventeen patients had no evaluable disease at median follow-up of 10 years.

Of the NCCTG patients, the great majority (73%) received 5-FU. With the introduction of irinotecan, oxaliplatin, bevacizumab, and cetuximab, median survival for patients with metastatic colon cancer has doubled.

Surgical series of patients with isolated liver disease have shown excellent median survivals (greater than 40 months) for the entire cohort [4]. In addition, many physicians will have anecdotal evidence of patients surviving long-term after ablation of isolated liver or lung metastases and without recourse to systemic chemotherapy. While approximately 30% of patients with isolated liver disease will be cured with resection, orthodoxy, particularly in the United States, has not favored offering patients liver resection or ablation unless there is curative intent. The most frequent explanation for the prolonged median survival for patients undergoing surgical resection is selection bias. However, another explanation could be that the intervention itself impacted survival in a positive manner, even in patients destined to die of their colon cancer.

I’d like to make two major points regarding the current North American approach to the treatment of metastatic colon cancer. First, we have had such a bias against surgical resection that it has prevented us from providing optimal care. In the Intergroup study (NCCTG 9741) of IFL (irinotecan, bolus fluorouracil, and leucovorin) versus FOLFOX (5-FU, leucovorin, and oxaliplatin) versus IROX (irinotecan and oxaliplatin), only 3% (24 patients) of the 795 patients enrolled had potentially curative resection attempted after chemotherapy [5, 6]. This low rate of resection occurred despite the fact that 37%–39% of patients had metastases limited to the liver or lung. A retrospective analysis of data in Sweden suggests that up to 10% of patients with metastatic colon cancer are eligible for complete surgical resection of metastatic liver disease [7]. Second, if we congratulate ourselves for achieving a complete response with chemotherapy, why should we not do this with nonsurgical ablative techniques? Patients achieving a complete response to first-line FOLFOX in the Intergroup N9741 trial had a median survival of 39 months, which was comparable with the group undergoing surgical resection and suggests that a logarithmic reduction in tumor cells by either method may be associated with prolonged survival. Despite oncologic orthodoxy arguing against it, should we re-examine the role of achieving a dramatic reduction in tumor cells by nonsurgical means? Nonsurgical approaches such as RFA, cryoablation, chemoembolization, and radiation (i.e., conformal techniques, proton beam, and nanoparticles) could provide benefit and will be briefly reviewed.

Ablation

The potential of RFA is illustrated by the recently published trial of Berber et al. [8]. In the period 1997–2002, 135 colon cancer patients with liver metastases that were judged unresectable underwent laparoscopic RFA. Few of these patients would have had second-line chemotherapy or have been exposed to newer combinations such as FOLFOX. Median survival in this series was 2.4 years. Multivariate predictors of survival include carcinoembryonic antigen (CEA) level >200, more than three lesions, and size of largest lesion: 3–5 cm or >5 cm. Among patients with a CEA level of 200 or less, the median survival was 2.8 years, compared with 1.3 years among patients whose higher CEA level (i.e., >200) values indicated a greater burden of disease (Table 1).

These survival figures bear comparison with those now being achieved using several lines of more sophisticated chemotherapy (Table 1) [8, 9]. Instead of quickly dismissing these differences as a result of selection bias, we should reappraise these results with the goal of rendering patients NED (no evidence of disease) by any means necessary. Several small series have now reported the successful use of RFA in patients with isolated pulmonary metastases [10], and RFA of other sites (such as bone, the adrenals, and kidney) is being pursued. Data from our institution indicate that RFA could be a standard of care for patients with small renal cell cancers, showing the potential of this approach in other tumors [11].

Given this background, the European Organization for Research and Treatment of Cancer trial 40004 planned to randomize 400 patients with unresectable liver metastases and no extrahepatic involvement to FOLFOX with or without RFA. However, the trial appears to be accruing slowly, perhaps because it is confined to patients with unresectable disease. The more appropriate issue is the potential impact of a broader approach to debulking in a wider range of patients, including those with limited extrahepatic involvement where a significant reduction in tumor cells can be achieved by liver resection.

Chemoembolization

Trials of chemoembolization conducted in the 1980s and 1990s report response rates ranging from 25%–100% [12]. The majority of patients had disease refractory to chemotherapy. Median survival ranged from 7–23 months [12]. The good survivals seen with chemoembolization compare well with E3200 and were probably not due to selection bias. For patients with significant liver metastases that are not amenable to surgical resection, should chemoembolization be offered in an attempt to reduce tumor burden?
Radiation therapy (which includes use of conformal techniques, proton beam, and nanoparticles) tends to be a treatment of last resort, confined to patients whose metastases are unresectable and too close to the bile ducts and portal vein to allow RFA.

Robertson et al. reported a series of 22 patients with unresectable liver metastases treated with between 48 and 72 Gy conformal radiotherapy [13]. Twenty-five percent of patients were free from hepatic progression at 1 year, and overall survival was 20 months. Proton beam therapy may be a more effective approach.

However, the use of nanoparticles holds promise [14, 15]. In a recent report, 21 patients with liver metastases were randomized to receive 5-FU/leucovorin with or without embolization of SIR (Selective Internal Radiation)–spheres (microspheres containing yttrium-90 in the hepatic artery) [14]. Among patients treated with the addition of microspheres, 8 of 11 had a partial response, whereas a partial response was seen in none of the patients in the control arm. Median survival was 29 versus 13 months, and time to progression was 18.6 versus 3.6 months.

This study was followed by a trial in 74 patients with unresectable liver metastases randomized to hepatic arterial infusion of floxuridine with or without yttrium-labeled microspheres [16]. Response rates were 44% with the microspheres and 18% without (p = .01), and 3-year survival was 17% versus 6.5% (Table 2).

In conclusion, if chemotherapy results in a logarithmic reduction in tumor cells and is associated with prolonged survival, what prevents us from applying this rationale to surgical or nonsurgical methods of reducing tumor burden? It is time to re-evaluate the current orthodoxy in North America that frowns upon these approaches. We should develop phase III trials evaluating RFA, chemoembolization, and radiation in an attempt to answer these questions and improve survival for our patients.

Disclosure of Potential Conflicts of Interest
D.P.R. has received support from Pfizer and Genentech.

References
2 Norton L. Conceptual and practical implications of breast tissue geometry: toward a more effective, less toxic therapy. The Oncologist 2005;10:370–381.

Table 1. Median survival of patients receiving RFA and those receiving chemotherapy

<table>
<thead>
<tr>
<th>Median survival</th>
<th>Berber et al. [8]</th>
<th>Hurwitz et al. [9]</th>
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<tr>
<td></td>
<td>RFA of liver metastases</td>
<td>IFL/placebo</td>
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<tr>
<td>All patients</td>
<td>2.4 years</td>
<td>16.6 months</td>
</tr>
<tr>
<td>Patients with CEA level &lt;200</td>
<td>2.8 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td>Patients with CEA level &gt;200</td>
<td>1.3 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA</td>
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</tbody>
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<sup>a p = .00003; b p = .01</sup>

Abbreviations: BV, bevacizumab; CEA, carcinoembryonic antigen; IFL, irinotecan/bolus fluorouracil/leucovorin; NA, not applicable; RFA: radiofrequency ablation.

Table 2. Patients with unresectable liver metastases, treated with hepatic arterial infusion of floxuridine with or without nanoparticles [16]

<table>
<thead>
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<th></th>
<th>Floxuridine + yttrium-labeled microspheres</th>
<th>Floxuridine</th>
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<tbody>
<tr>
<td>Response rate</td>
<td>44%</td>
<td>18%</td>
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<tr>
<td>Time to progression</td>
<td>15.9 months</td>
<td>9.7 months</td>
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<tr>
<td>1-year survival</td>
<td>72%</td>
<td>68%</td>
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<tr>
<td>3-year survival</td>
<td>17%</td>
<td>6.5%</td>
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<tr>
<td>5-year survival</td>
<td>3.5%</td>
<td>0%</td>
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