Cancer treatment-induced mucositis

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Gyu Seok Cho, M.D., Ph.D.

Abstract
Cancer treatment-induced mucositis is a common and dose-limiting side effect of chemotherapeutic agents, radiotherapy, and biologic therapies. Clinicians and researchers continue to develop new strategies for mucositis prophylaxis and treatment. Here, we summarize new mucositis prevention and treatment strategies, including a review of the evidence for systemic drugs and biologic therapies, new mucositis prevention strategies, new mucositis treatment strategies, and an update on mucositis research.

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Introduction
It has been hypothesized that clinical state of oligometastatic disease in some patients with a limited number of clinically detectable metastatic tumors, is somewhat transitional between those of localized and widespread systemic disease. In this state, local control (LC) of oligometastases may allow better systemic control.

Unlike the majority of other cancers, colorectal carcinoma (CRC) often presents a solitary metastasis or oligometastases, which are most frequently located in the liver or lung. These tendencies have encouraged aggressive surgical approaches to the treatment of patients with CRC metastases. Long term results from retrospective analysis of patients with CRC metastases to liver or lung treated by resection show 5-year overall survival rates of approximately 30–40%. The percentage of patients, however, amenable to surgery fall in the range 10–25%. Therefore, non-surgical invasive, ablative methods, such as cryotherapy, laser–induced interstitial thermotherapy, and radiofrequency ablation (RFA) have been evaluated in retrospective trials as alternative local treatments. As non-invasive method, furthermore, recently developing precise radiation therapy including stereotactic body radiotherapy (SBRT) can be offered to patients unable to tolerate invasive procedures, or when tumors are situated in areas in which invasive procedures would result in unacceptable morbidity. Recently, phase I/II reports of SBRT (0, 11) on liver or lung metastasis from variable primary cancers treated have achieved greater than 90% local control at 2 years. Higher dose to target volume allows higher local control of tumors and might prolong survival among patients with the oligometastases. Since 2001, the Korea Cancer Center Hospital has used 3 fractions SBRT to treat patients with oligometastases. The outcomes for CRC patients treated for regional failure, liver metastasis, or lung metastasis at our institute have been recently published (12–15). Herein, we reviewed oligometastases in the lung, liver or pelvic/pelvic lymph node from CRC treated by SBRT of high dose 0 = 45 Gy/3 frac according to survival and local control.

Materials & Results
We retroactively reviewed 41 patients with 50 lesions confined to one organ from CRC treated with high dose SBRT ≥ 45 Gy between 2003 and 2009.

Three-year OS, disease progression free survival and local control (LC) rates were 60%, 60% and 64%, respectively. Five-year OS, disease progression free survival and LC rates were 38%, 40% and 57%, respectively (Fig 1). On univariate analysis, cumulative gross tumor GTV ≤ 17
ml and SBRT dose ≥ 48 Gy were significantly favorable prognostic factors for LC (p=0.02). During follow-up, 23 of 41 patients (56%) experienced disease progression. Fourteen patients had local failure, 15 patients had regional failure and 14 patients had distant metastases. The most frequent failure occurred in non-targeted regional site and nine patients had all recurrences in local, regional and distant sites. After recurrence, patients underwent additional salvage or palliative treatments according to the type of failure. All patients tolerated the high dose SBRT treatment. Seventeen patients (41%) experienced nausea, vomiting and musculoskeletal discomfort of grade 1 or 2 during treatment. Three patients (7%) experienced severe late complication above grade 3 and details for patients are described in Table 1.

**Table 1.** Details for three patients with severe complications above grade 3

<table>
<thead>
<tr>
<th>Site</th>
<th>SBRT dose</th>
<th>Toxicity</th>
<th>Clinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paravertebral LN</td>
<td>48 Gy</td>
<td>Intestinal Abdominal pain developed at 1</td>
<td>Oligometastases confined one organ for colorectal cancer treated by SBRT. Clin Exp Metastasis 27:273-278</td>
</tr>
<tr>
<td>Pelvic LN</td>
<td>51 Gy</td>
<td>Intestinal Abdominal pain developed at 1</td>
<td>Colorectal Oligometastases Treated by Stereotactic Body Radiotherapy48 Mi Sook Kim</td>
</tr>
</tbody>
</table>

**Discussion & conclusions**

Regression is regarded as the standard curative treatment in patients with pelvic recurrence, liver or lung metastases from CRC. For inoperable patients, RFA is a common alternative to local treatment for liver or lung metastases and reported 5-year survival rate of 20−50%. Data on SBRT in patients with colorectal oligometastases, as another local modality for nonsurgical candidates, are limited, with few studies reporting on long term survival. Table 4 shows the recently published large surgical series in patients with LN metastases, who had 5-year survival rate of 30−40%, and in patients with liver or lung metastases, who had 5-year survival rate of 40−50%. Current study has reported 5-year survival of 38% in patients with colorectal oligometastases, which is comparable result with surgery series. Generally, tumor size is a prognostic factor for local control or survival. RFA showed improved local control with smaller sized metastases. Gillams AR and Lees WR reported that 5-year survival rate was 24% for 153 patients with 5 or less metastases of maximum diameter ≤ 5 cm and no extrahepatic disease and 33% for 69 patients with 3 or less tumors of ≤ 3.5 cm in diameter. Some SBRT studies reported that GTV was a significant factor for local control or survival.03,14,26,27 Current study showed improved local control with cGTV ≤ 17 ml of 83% at 5 years. Recent SBRT study of liver metastases and early stage NSCLC also showed good local control rate of19 90% in patients with tumor < 3–4 cm.(33,29) Considering good local control of SBRT in small size tumor and low morbidity, SBRT could be an alternative treatment of surgery in small sized colorectal oligometastases. However, cGTV 71ml showed poor local control of 29% at 5 years. To improve local control in large sized colorectal oligometastases, further study should be need.

**Table 2.** Selected published series of solitary or oligometastases from colorectal cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>site</th>
<th>No. of patients</th>
<th>Median fu time (months)</th>
<th>Overall survival rates (%)</th>
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<tbody>
<tr>
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<td>LN</td>
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<td>NA</td>
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<td>31</td>
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<td>2005</td>
<td>Liver</td>
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<td>74</td>
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<td>Surgery*</td>
<td>2003</td>
<td>Lung</td>
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<tr>
<td>Surgery*</td>
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<td>Lung</td>
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<td>29</td>
<td>53</td>
</tr>
<tr>
<td>RFA*</td>
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<td>RFA*</td>
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<td>Lung</td>
<td>100</td>
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<td>SBRT</td>
<td>2010</td>
<td>Lung, Liver, LN, bone, brain</td>
<td>59</td>
<td>32</td>
<td>48</td>
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<tr>
<td>Current study</td>
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<td>Lung, Liver, LN</td>
<td>41</td>
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<td>60</td>
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<tr>
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<td>Radiation induced Hemorrhage</td>
<td>12 months after SBRT</td>
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<tr>
<td>Para-aortic</td>
<td>48 Gy</td>
<td>Intestinal ulceration</td>
<td>8 months after SBRT, patient received small bowel resection</td>
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<tr>
<td>Pelvic LN</td>
<td>51 Gy</td>
<td>Intestinal ulceration</td>
<td>1 month after SBRT, patient received colostomy</td>
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<th>Study Year</th>
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<th>Overall survival rates (%)</th>
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<th>At 5 year</th>
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<td>N/A</td>
<td>N/A</td>
<td>27</td>
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<tr>
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<td>LN</td>
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<td>N/A</td>
<td>45</td>
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<td>2003</td>
<td>Liver</td>
<td>1001</td>
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Materials and results: Between 2003 and 2009, total of 41 patients with 50 lesions confined to one organ from colorectal cancer and treated with high dose SBRT above 45 Gy or more were involved in. The metastatic organs were the lymph node (18 patients), lung (12) and liver (11). SBRT doses ranged from 45 to 60 Gy in 3 fractions (median 48 Gy). The 3-year local control and overall survival rates were 64% and 60%, and the respective 5-year rates were 57% and 38%. Cumulative gross tumor volume and SBRT dose were statistically significant prognostic factors for local control. The grade 3 or 4 intestinal complications occurred in 3 patients (7%) to receive 48 or 51 Gy.

Conclusions: High dose SBRT $\geq$ 45 Gy for oligometastases from CRC showed comparable result with surgical series. For improvement of local control, higher dose $\geq$ 48 Gy is recommend when possible. However, considering severe complications above grade 3 occurred in $\geq$ 48 Gy, further study will be required to define the optimal constraint for normal tissue such as intestine.
Colorectal Oligometastases Treated by Stereotactic Body Radiotherapy

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