WHITE PAPER – Stereotactic Body Radiotherapy (SBRT) for Liver Metastasis

I. Introduction

This white paper will focus on treatment of liver lesion with stereotactic radiosurgery that are mostly metastatic. Sections one through six (**I – VI**) consist of a general review of liver metastases and more information from the National Cancer Institute can be found at **cancer.gov**. Because carcinoma of the colon is the most common cancer to metastasize to the liver, this paper will focus mainly on information from the National Cancer Institute's information on Colon Cancer. Section seven (**VII**) will then provide a literature review on stereotactic radiosurgery for hepatic metastasis and section eight (**VIII**) (for society members only) will provide clinical indications and treatment guidelines on stereotactic radiosurgery for metastatic disease of the liver.

II. Definition and Incidence

The most common metastatic lesion in the liver is from colorectal adenocarcinoma, as approximately 50% of colon cancer patients will be diagnosed with hepatic metastases, either at the time of initial presentation or as a result of disease recurrence. This is approximately 50,000 patients per year, half of whom have the liver as the only site of known metastatic disease[1]. If untreated, 3-year survival is 3% with no survivors at the 5 year time point. [2]

III. Prognostic Factors

Liver metastasis from a primary cancer is by definition, evidence that the cancer has spread and may or may not be resectable. For patients with hepatic metastasis considered to be resectable (based on limited number of lesions, intrahepatic locations of lesions, lack of major vascular involvement, absent or limited extrahepatic disease, and sufficient functional hepatic reserve), a negative margin resection has resulted in 5-year survival rates of 25% to 40% in mostly nonrandomized studies.[3 4 5 6 7 8] Improved surgical techniques and advances in preoperative imaging have allowed for better patient selection for resection.

IV. Cellular Classification

Cellular classification again depends on the primary cancer. Histologic types of colon cancer that may metastasize to the liver include the following: Adenocarcinoma (most colon cancers).

- Mucinous (colloid) adenocarcinoma.
- Signet ring adenocarcinoma. Scirrhous tumors. Neuroendocrine*.[9]

** Note: Tumors with neuroendocrine differentiation typically have a poorer prognosis than pure adenocarcinoma variants.*

V. Staging

By definition staging for metastatic liver disease is Stage IV with additional classification depending on the primary tumor.

VI. Treatment Options

Although only a small proportion of patients with hepatic metastases are candidates for surgical resection, advances in tumor ablation techniques and in both regional and systemic chemotherapy administration provide for a number of treatment options. Patients with hepatic metastases that are deemed unresectable will occasionally become candidates for resection if they have a good response to chemotherapy. These patients have 5-year survival rates similar to patients who initially had resectable disease.[11] Radiofrequency ablation has emerged as a safe technique (2% major morbidity and <1% mortality rate) that may provide for long-term tumor control. [12 13 14 15 16 17 18 19] Radiofrequency ablation and cryosurgical ablation [20 21 22 23] remain options for patients with tumors that cannot be resected and for patients who are not candidates for liver resection.

Other local ablative techniques that have been used to manage liver metastases include embolization and interstitial radiation therapy.[24] [25] Patients with limited pulmonary metastases, and patients with both pulmonary and hepatic metastases, may also be considered for surgical resection, with 5-year survival possible in highly-selected patients.[26 27 28]

Systemic Therapy

Systemic therapy is generally the standard of care for metastatic disease. The type, combination duration and frequency of chemotherapy and its sequencing sin relation to local liver directed therapy varies with each cancer type.

With liver metastasis from colorectal cancer being the most common primary – the role of systemic therapy for liver metastasis from colorectal cancer is discussed here.

The role of adjuvant chemotherapy after potentially curative resection of liver metastases is uncertain. A trial of hepatic arterial fluorouracil plus systemic fluorouracil (5-FU) plus leucovorin was shown to result in improved 2-year disease-free survival and overall survival (OS) (86% vs. 72%, P = .03), but did not show a significant statistical difference in median survival, compared with systemic 5-FU therapy alone.[29] A second trial preoperatively randomized 109 patients who had one to three potentially resectable colorectal hepatic metastases to, either no further therapy or postoperative hepatic arterial floxuridine plus systemic 5-FU. [30] Of those randomized, 27% were deemed ineligible at the time of surgery, leaving only 75 patients evaluable for recurrence and survival rates. While liver recurrence was decreased, median or 4-year survival was not significantly different. Further studies are required to evaluate this treatment approach and to determine if more effective systemic combination chemotherapy alone may provide similar results compared with hepatic intra-arterial therapy plus systemic treatment.

Hepatic intra-arterial chemotherapy with floxuridine for liver metastases has produced higher overall response rates but no consistent improvement in survival when compared to systemic chemotherapy. [31] [32] [33] [34] [35] Controversy regarding the efficacy of regional chemotherapy has led to initiation of a large multicenter phase III trial (CALGB-9481) of hepatic arterial infusion versus systemic chemotherapy. The use of the combination of intra-arterial chemotherapy with hepatic radiation therapy, especially employing focal radiation of metastatic lesions, is under evaluation. [36] Several studies show increased local toxic effects with hepatic infusional therapy, including liver function abnormalities and fatal biliary sclerosis.

Currently, there are seven active and approved drugs for patients with metastatic colorectal cancer: 5-FU, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab. When 5-FU was the only active chemotherapy drug, trials in patients with locally advanced, unresectable, or metastatic disease demonstrated partial responses and prolongation of the time-to-progression (TTP) of disease, [37] [38] as well as improved survival and quality of life for patients receiving chemotherapy, compared with the best supportive care. [39] [40] [41] Several trials have analyzed the activity and toxic effects of various 5-FU-leucovorin regimens using different doses and administration schedules and showed essentially equivalent results with a median survival time in the 12-month range.[42] Prior to the advent of multiagent chemotherapy, two randomized studies demonstrated that capecitabine was associated with equivalent efficacy when compared with the Mayo Clinic regimen of 5-FU-leucovorin. [43] [44]

Drug combinations for metastatic colorectal carcinoma are described in further detail at **Cancer.gov**:http://www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional/page1

The Addition of Targeted Therapy to Multiagent Chemotherapy

Bevacizumab

At least 3 prospective studies have now shown that the addition of Bevacizumab to multiagent chemotherapy improved progression free and overall survival in these patients.[45] [46] [47] However there are currently no completed randomized controlled studies evaluating whether continued use of bevacizumab in the second line or third line after progressing on a first-line bevacizumab regimen is worthwhile.

Cetuximab/panitumumab and second-line chemotherapy

Cetuximab is a partially humanized monoclonal antibody against the epidermal growth factor receptor (EGFR). Panitumumab is a fully humanized antibody against the EGFR. For patients who have progressed on irinotecan-containing regimens, a randomized phase II study was performed of either cetuximab or irinotecan and cetuximab. The median TTP for patients receiving cetuximab was 1.5 months, and the median TTP for patients receiving irinotecan and cetuximab was 4.2 months. On the basis of this study, cetuximab was approved for use in patients with metastatic colorectal cancer refractory to 5-FU and irinotecan.[48] Retrospective studies of patients with metastatic colorectal cancer have suggested that responses to anti-EGFR antibody therapy are confined to patients with tumors that harbor wild types of KRAS (i.e., lack activating mutations at codon 12 or 13 of the KRAS gene).[49] Importantly, patients with mutant KRAS tumors may experience worse outcome when cetuximab is added to multiagent chemotherapy regimens containing bevacizumab.

VII. SBRT Literature Review

This section reviews the literature associated with stereotactic radiosurgery (SRS), at times, also called stereotactic body radiation therapy, of liver metastasis. SRS is defined here as a high dose of radiation per treatment with a small number of total treatments (up to a maximum of five).

Historically, hepatic radiotherapy has been limited due to the low tolerance of the whole liver to radiation and the potential for radiation induced liver disease (RILD).[50] Advanced techniques such as conformal dosing and image guidance have allowed for the delivery of focal ablative doses of radiation with the sparing of normal tissue. Dose escalation studies with fractionated regimens of radiation have shown a clear dose response for primary cancers of the liver and liver metastases.[51 52 53]

SRS of the abdomen has also been limited by the movement of intra-abdominal organs that naturally occurs with respiration. There have been several methods to eliminate or modify this movement in order to ensure that the high-dose region coincides with the tumor and does not inadvertently treat normal tissue.[54 55] Some of these techniques include respiratory gating, active breathing control, deep inspiration breath hold, abdominal compression, or some combination. Products with dynamic motion tracking offer some obvious advantages in patient comfort and possibly in precision.

Within the last decade, SRS techniques have been increasingly applied to the treatment of liver tumors, further refining the ability to target the tumor and minimize toxicity to normal tissue.[56 57] Because of the spatial precision of SRS, it is feasible to administer a high radiation dose in only a few treatments. By minimizing the amount of radiation to surrounding healthy tissue, it is possible to decrease the rate of toxic liver complications and RILD and increase the radiation dose to cancerous tissue, thereby allowing for better local control. However, acute and long term complications can still occur.[58]

There have been several publications of SRS for liver lesions in the literature with encouraging results. The earliest report was from 1995 in Stockholm, Sweden where investigators reported on the results of the first 42 extracranial treated tumors in 31 patients. Most of the patients had solitary tumors in the liver, lung or retroperitoneal space. Clinical target volumes ranged from 2 to 622 cm3 (mean 78 cm3) with radiation doses of 7.7 to 30 Gy per fraction (mean 14.2 Gy) given on 1 to 4 occasions. They observed a local control rate of 80% with no progressive disease during a follow-up period of 1.5 to 38 months. In addition, fifty percent of the tumors decreased in size or disappeared.[59]

In 1998 the same group reported their experience with SRS for primary and metastatic liver tumors, treated with 15 to 45 Gy, delivered in one to five fractions in 75 evaluable tumors in 50 patients. Volumes treated ranged from 2 cm3 to 732 cm3 (mean, 73 cm3). With a mean follow-up time of 12 months (range 1.5 to 38 months) approximately 30% of tumors demonstrated growth arrest, nearly 40% were reduced in size, and 32% disappeared in imaging studies. Four of the tumors were classified as local failures (5.3%).[60] Unfortunately, the mean survival time was only 13.4 months (range 1.5 to 39 months), with the predominant cause of death related to progressive liver cirrhosis and progression of extrahepatic disease. Another more recent study by the same group treated patients with liver only recurrences after liver resection. The patients received 20 Gy in two fractions or 15 Gy in three fractions to the tumors with limited side effects. Thirteen to 101 months

later, all treated tumors were locally controlled with complete radiologic remission of two of them. Only one patient recurred in the liver, with bilobar lesions preceded by extrahepatic spread. One patient died later tumor-free from stroke, two died from generalized tumors, and one patient remains in remission 101 months after stereotactic radiosurgery.[61]

In 2001, Herfarth *et al.* from Heidelberg, Germany performed a Phase I/II dose-escalation trial of single dose SRS in 37 patients with 60 liver lesions, the majority of which were metastases.[62] The dose was escalated from 14 Gy to 26 Gy with a median tumor size of 10 cm3 (range, 1 to 132 cm3). All patients tolerated the treatment well without any major side effects. Eleven patients experienced intermittent loss of appetite or mild nausea for 1 to 3 weeks after treatment. None of the treated patients developed clinically detectable RILD. Follow-up data was obtained from 55 treated tumors in 35 patients and the median follow-up period was 5.7 months (range 1.0 to 26.1 months). Fifty-four of 55 tumors (98%) were locally controlled after 6 weeks based on CT findings (22 cases of stable disease, 28 partial responses, and 4 complete responses). After a dose-escalating and learning phase, the actuarial local tumor control rate was 81% at 18 months after therapy. A total of 12 local failures were observed during follow-up. The longest local tumor control was 26.1 months. The authors concluded that SRS via a single-dose is a feasible method for treatment of singular inoperable liver metastases with the potential of a high local tumor control rate and low morbidity.

Wulf *et al*. reported the experience from the University of Wurzburg of 5 patients with primary liver cancer and 39 patients with 51 hepatic metastases treated by SRS since 1997. Twenty-eight targets were treated in a "low-dose" group with 10 Gy in 3 fractions (n = 27) or 7 Gy in 4 fractions (n = 1). In addition, there was a "high-dose" group where patients were treated with 12 to 12.5 Gy in 3 fractions (n = 19) or 26 Gy in a single fraction (n = 9). Median follow-up was 15 months (2 to 48 months) for primary liver cancer and 15 months (2 to 85 months) for hepatic metastases. All primary liver cancers were controlled. There were nine local failures (3 to 19 months) of the 51 metastases. There was a borderline significant correlation between dose and local control (p = 0.077) with the actuarial local control rate after 12 and 24 months at 86% and 58% in the low-dose-group versus 100% and 82% in the high-dose-group. There were no Grade 3 or higher toxicities.[63] In multivariate analysis, high versus low-dose was the only significant factor predicting local control (p = 0.0089). Overall survival after 1 and 2 years was 72% and 32% for all patients. The authors concluded that SRS of primary liver cancer and hepatic metastases offers a locally effective treatment without significant complications in patients who are not amenable for surgery.

A Phase II study by Hoyer *et al*. reported the results of SRS for the treatment of colorectal metastases. Sixty four patients with a total of 141 colorectal metastases in the liver (n=44) or elsewhere (n=20) were treated with 15 Gy in 3 fractions within 5 to 8 days.[64] Median follow up was 4.3 years and after 2 years actuarial local control was 86% in tumor based analysis and 63% in patient based analysis. Survival rates were 22% at 3 years and 13% at 5 years. Toxicity was in most cases mild however there were three serious adverse events and one death. In general the authors concluded that SRS for inoperable colorectal metastases compares to other methods of local ablation for metastases and offers promising local control.

More recently, Schefter *et al*. reported the early results of a multicenter Phase I study of SRS for liver metastases.[65] Eligible patients had one to three liver metastases with tumor diameters of <6 cm, and adequate liver function. The first cohort received 36 Gy in three fractions. Subsequent cohorts

received higher doses up to a chosen maximum of 60 Gy in 3 fractions. At least 700 mL of normal liver had to receive a total dose <15 Gy. Dose-limiting toxicity was defined as acute Grade 3 liver or intestinal toxicity or any acute Grade 4 toxicity. Eighteen patients were enrolled with 4 patients having multiple tumors. No patient experienced a does limiting toxicity, thus the dose was escalated to 60 Gy in three fractions. Twelve of the 18 patients were alive at the time of their analysis, a median of 7.1 months after enrollment in the protocol.

This study was continued and in 2006, Kavanagh *et al.* reported on an interim analysis of this prospective Phase I/II study of SRS for liver metastases. Here, eligible patients with liver metastases had a maximum tumor diameter < 6 cm and 3 or fewer discrete lesions. In addition they had treatment planning confirm that 700 mL of normal liver was to receive a total dose <15 Gy. The tumor received 60 Gy in 3 fractions over 3 to 14 days in the Phase II component of the trial. In the interim analysis in July of 2006, 36 patients had been enrolled: 18 in Phase I and 18 in Phase II. Among the 21 patients with at least 6 month follow-up (range 6 to 29), there was one instance of SRS-related grade 3 toxicity which occurred in the subcutaneous tissue superficial to the liver. No grade 4 toxicity occurred. They found that for 28 discrete lesions treated, the 18 month actuarial local control rate estimate was 93%.[66]

Most recently, Rusthoven *et al.* published the final results of this multi-institutional phase I/II trial of SRS for liver metastases.[67] For the 49 assessable and discrete lesions that were treated the authors found local control to be 92% with only 2% of patients experiencing Grade 3 or higher toxicity at a median follow up time of 16 months. Local progression occurred in only three lesions at a median of 7.5 months after SRS. This is the highest published result for local control although survival at 2 years was still only 30%. The authors concluded that SRS treatment of 60 Gy given in 3 fractions was both safe and effective for patients with one to three hepatic metastases. Indeed this treatment can be seen as an emerging standard of care for patients with liver metastasis.

VIII. Clinical Indications and Guidelines for SBRT

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