Timing of Initiation of Chemotherapy after Primary Colorectal Cancer Resection

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1 Introduction

Colorectal cancer (CRC) is the third leading cause of cancer mortality in the Western world (Parkin et al., 2005). While surgical resection remains the cornerstone of management for patients with stage I–III disease, a considerable proportion of patients will ultimately relapse and die from their disease. Large, randomized clinical trials of adjuvant chemotherapy (AC) after curative resection of CRC have consistently demonstrated improvement in survival, which dictates the current standard of care (National Institutes of Health, 1990). Adjuvant chemotherapy is routinely recommended after curative surgical resection of stage II and III rectal cancer, stage III (node-positive) colon cancer, and stage II (node-negative) colon cancer in which high-risk features are present (Benson et al., 2004; Figueredo et al., 2004). However, the optimal time from surgery to the start of chemotherapy in CRC is not known.

The surgical resection of asymptomatic primary colorectal cancer with unresectable synchronous metastases is controversial. Among patients with severe intestinal symptoms, resection is mandatory before starting systemic chemotherapy (Joffe et al., 1981; Longo et al., 1988; Rosen et al., 2000). Palliative resection of the primary tumor is also reported to improve the efficacy of systemic chemotherapy (Temple et al., 2004) and prolong the duration of chemotherapy (Kaufman et al., 2008). A recent review article suggested that noncurative resection of asymptomatic primary colorectal tumors may prolong survival in patients with metastatic colorectal cancer (Eisenberger et al., 2008). However, another article concluded that chemotherapy should be started initially, with resection of the primary tumor reserved for the small proportion of patients who develop major complications from the primary tumor. This is because resection of an asymptomatic primary tumor provides only minimal palliative benefits (Scheer et al., 2008). The National Comprehensive Cancer Network currently recommends that patients with metastatic colorectal cancer undergo surgical intervention if they have a bowel obstruction, an impending obstruction, or metastases that are potentially resectable.

The purpose of the surgical resection of primary tumors is the prevention of hemorrhage, perforation, and bowel obstruction. In many cases, patients cannot continue chemotherapy treatments because of complications such as bleeding, perforation, and bowel obstruction when chemotherapy is initiated without prior surgical resection of the primary tumor. Surgical removal of the primary tumor therefore seems necessary to continue chemotherapy with few complications. In the past, some investigators have recommended routine resection of the primary tumor to prevent the need for urgent surgical procedures because of local complications (Joffe et al., 1981; Longo et al., 1988). Ruo reported that 30 (29%) of the 103 patients who were initially managed without bowel resection required a subsequent surgery for the palliation of complications (Ruo et al., 2003). Recently, some authors have suggested the elective resection of asymptomatic colorectal cancers in at least a subset of patients with less advanced stage IV disease (Rosen et al., 2000; Ruo et al., 2003). Other authors have suggested deferring the resection of minimally symptomatic colorectal tumors because most of these patients succumb to progressive systemic disease rather than complications related to the intact primary lesion (Ruo et al., 2003; Benoist et al., 2005; Yoshida et al., 2011). However, surgical resection may delay the start of chemotherapy (Benoist et al., 2005). Generally, an interval of 4 weeks after surgery is considered necessary before the initiation of chemotherapy treatments such as folinic acid, fluorouracil (5-FU), and oxaliplatin (FOLFOX); folinic acid, 5-FU, and irinotecan (FOLFIRI); and capecitabine and oxaliplatin (XELOX). Most clinical trials exclude patients who have undergone an operation within 4 weeks. However, there is no apparent evidence for this delay. A metastatic tumor can grow rapidly before the start of chemotherapy and possibly lead to patient death (Figure 1).
Before               After

Figure 1: Liver metastases before and after resection of primary colon cancer. (Borrowed from Dr. Kohei Shitara)

Because the significance of this postoperative 4-week delay before the start of chemotherapy is unclear, we evaluated the feasibility and safety of an early chemotherapy start in patients who had undergone colorectal surgery for colorectal cancer and who had multiple, distant, synchronous metastases.

2 Demerit of Resection

It was recently reported that the growth rate of liver metastases was significantly higher in patients in whom the primary colorectal tumor had been resected than in patients in whom the primary tumor was still in situ (Peeters et al., 2004; Simpson-Herren et al., 1976). In addition, immunohistochemical analysis revealed an increased proliferation rate and increased vessel density in the metastases in the absence of the primary tumor. These data suggest that outgrowth of metastatic disease may be partially controlled by the primary tumor (Peeters et al., 2006). In animal models, primary tumor-mediated inhibition of metastatic vascularization and outgrowth is an established concept in tumor biology. Research in this area was initiated by the observation that in the Lewis lung carcinoma mouse model, resection of the primary tumor led to increased vascularization and accelerated growth of distant metastases that had previously remained microscopic. O’Reilly et al. demonstrated in a murine model that the primary tumor produced the potent antiangiogenic compound angiostatin, which prevented vascularization and thereby the growth of metastases (O’Reilly et al., 1994). More recently, it was demonstrated that irradiation of murine angiostatin-producing primary tumors was subsequently followed by rapid growth of the metastases, suggesting a similar phenomenon (Camphausen et al., 2001; von Essen., 1991). Moreover, when angiostatin was replaced immediately after regression of the primary tumor, outgrowth of the metastases did not occur (Camphausen et al., 2001).

Although only a limited number of patients were included, a significant increase in \(^{18}\text{F}-\text{FDG}\) uptake of colorectal liver metastases after resection of the primary tumor (Scheer et al., 2008). In contrast, \(^{18}\text{F}-\text{FDG}\) uptake in liver metastases remained stable in 2 subsequent \(^{18}\text{F}-\text{FDG}\) positron emission tomography (PET) scans of patients without any surgery or other therapeutic intervention between the scans. These results suggest that in humans, as in animal models, the primary tumor can inhibit the growth of its metastases. This inhibitory effect on secondary tumor growth is reversed when the primary
tumor is resected. For example, Li et al. demonstrated increased microvessel density, a higher cell proliferation index in tumor cells, and a decreased apoptotic index after resection of a primary tumor in a mouse model compared with a sham operation (Li et al., 2001).

On the other hand, the increased metabolic activity observed after resection of the primary colorectal tumor may also be caused by the surgical trauma of the resection itself. Surgery alone could stimulate proinflammatory cytokines (interleukin-6 (IL-6) and IL-1β) resulting in enhanced expression of vascular endothelial growth factor and angiogenesis (Nagengast et al., 2007). The data cannot differentiate between these 2 hypotheses. Another explanation for the outgrowth of the metastases could be that the increase in 18F-FDG uptake is merely time-dependent progression, and that synchronous liver metastases (group A) would grow faster than metachronous liver metastases (most patients in group B). This explanation, however, is unlikely because the initial standard uptake values (SUVs) in both groups were identical and the interval between the 2 serial 18F-FDG positron emission tomography (PET) scans was even longer in group B than in group A. Furthermore, increased retention of 18F-FDG may be the result of the increased size of the lesion; however, our results did not show a correlation between the alteration in tumor size and the change in SUV.

Although the precise mechanism of increased metabolic activity after resection of the primary colorectal tumor—as observed in our study—remains to be clarified, the slowing of this accelerated growth by angiogenesis inhibitors seems promising. The present approach of serial 18F-FDG PET scans before and after resection of the primary tumor would possibly allow direct measurement of the therapeutic effect of such antiangiogenic therapy. Such studies might provide insight into the use of adjuvant antiangiogenic agents to prevent accelerated outgrowth of distant metastases after resection of the primary colorectal tumor.

3 5-FU

Surgeons are reluctant to prescribe 5-FU in the immediate postoperative period. This is primarily because of the belief that 5-FU will increase the anastomotic leakage rate. This can result in the need for reoperation, the creation of a colostomy, and the need for a future takedown, or even death. It is estimated that 1 out of 3 postoperative deaths after colonic surgery are caused by leaking anastomosis (Debas et al., 1972). The dangers of postoperative 5-FU are well documented. Several animal studies have reported weaker anastomosis and an increased risk of anastomotic rupture when systemic 5-FU is given as a bolus immediately after surgery (Goldman et al., 1969; Morris., 1979). Immediate intraperitoneal 5-FU also increases the risk of anastomotic dehiscence (Weiber et al., 1994). Continuous infusion of 5-FU allows higher daily dosages and appears to be safer than bolus 5-FU (Lokich et al., 1989). Continuous infusion avoids the peak serum levels of 5-FU that are caused by bolus dosing, and it may therefore be effective for colorectal cancer without increasing the rate of anastomotic leakage. The oral fluoropyrimidine, UFT, and capecitabine have been developed to improve tolerability and patient convenience and have replaced the continuous infusion of 5-FU in many treatment regimens (Bennouna et al., 2009). Oral fluoropyrimidine is a promising alternative to the constant infusion of 5-FU, and pharmacokinetic studies have found that consecutive oral administrations of UFT as tegafur (370 mg·m⁻²·d⁻¹) provide a steady-state concentration of 5-FU that is comparable to that achieved by a 5-day constant infusion at 250 mg·m⁻²·d⁻¹. In addition, injecting a bolus of 5-FU results in ultra-high concentrations followed by rapid disappearance (Ho et al., 1998; Borner et al., 2002). We therefore selected the XELOX regimen for this study.
Adjuvant Chemotherapy for CRC

The amount of time before the initiation of AC is an important parameter. Timely access to AC is often cited and tracked as a quality indicator (Systemic treatment wait times. 2011). Furthermore, beyond a certain time period after surgery, such as the often-quoted 12 weeks, it is uncertain whether the adjuvant benefit diminishes or is even lost entirely. To address this important gap in the literature, we undertook a formal systematic literature review and a meta-analysis to identify studies that assessed the relationship between time to AC and survival in CRC.

The effect of AC on survival is thought to be the eradication of micrometastatic deposits in a proportion of patients who would otherwise eventually experience cancer recurrence. There is a substantial theoretical rationale to the prompt initiation of AC after curative surgery. Studies in animal models suggest that surgery may increase the numbers of circulating tumor cells and potentiate the growth of metastatic deposits. This increase in metastatic growth is thought to correlate with a reduction in angiogenesis inhibitors such as angiostatin following removal of the primary tumor (McCulloch et al., 1994; Filder et al., 1994; Folkman et al., 1990; Gunduz et al., 1979). Surgery has also been shown to enhance production of oncogenic growth factors such as transforming growth factor α that can increase tumor growth (Ono et al., 1994; Eggermont et al., 1987). Furthermore, the classic mathematical model by Goldie and Coldman predicts that the probability of mutations that lead to drug resistance increases over time (Goldie et al., 1979) and is dependent on mutation rate and tumor size. Whether the more recent discovery of pluripotent colon cancer stem cells may also play a role in relapse following AC awaits further investigation (Dalerba et al., 2007; O’Brien et al., 2007; Ricci-Vitiani et al., 2007).

If we apply the findings to a patient who is ready to initiate AC 4 weeks after surgery but is delayed for logistical rather than medical reasons, that patient would have a 14% increased risk of mortality if treated at 8 weeks and a 30% increased risk of mortality at 12 weeks (James et al., 2011). The following hypothetical example makes use of Adjuvant! Online to illustrate the potential effect that the time-to-AC parameter may have on patient outcome (Adjuvant! Online. 2010): a 65-year-old man in good general health, with T3N2 moderately differentiated colon cancer is treated with fluorouracil-based chemotherapy and has an estimated 5-year survival probability of 60%. If we assume this estimate is made on the basis of a time to AC of 4 weeks (which is reasonable because Adjuvant! Online is based on clinical trials that have strict time-to-AC limits), then a delay to 8 weeks and to 12 weeks would reduce his 5-year survival prognoses to 54% and 48%, respectively. In perspective, the survival effect of a shorter time to AC would be comparable to the magnitude of benefit seen with the addition of oxaliplatin to fluoropyrimidine chemotherapy in the adjuvant setting (André et al., 2004; Kuebler et al., 2007).

Bevacizumab

Wound-healing complications with bevacizumab therapy were first recognized during the pivotal phase III trial of bevacizumab, which was conducted in 813 previously untreated patients with metastatic colorectal cancer (Hurwitz et al., 2004). The control arm of the study comprised patients who received irinotecan, 5-FU, and leucovorin (LV), while the treatment arm added bevacizumab as targeted therapy. In patients who underwent surgery after beginning study treatment, 15% (6/39) of patients in the treatment arm experienced wound healing or bleeding complications, compared with 4% (1/25) in the control arm (Avastin prescribing information. 2010). To investigate how the interval between bevacizumab therapy...
and surgery affects the risk of wound-healing complications, Scappaticci et al. performed a meta-analysis that included patients from the pivotal phase III trial (Scappaticci et al., 2005), as well as patients from a trial comparing 5-FU and LV with or without bevacizumab (Kabbinavar et al., 2005). In patients who underwent surgery after beginning study treatment, 3.4% (1/29) experienced wound-healing complications in the arm receiving chemotherapy alone compared with 13% (10/75) of patients receiving bevacizumab and chemotherapy; however, this difference did not reach significance (P < .28). Of the 10 patients who experienced wound-healing complications after surgery with bevacizumab and chemotherapy, the time interval between bevacizumab and surgery was 0 to 29 days for 5 patients and 30 to 59 days for 5 patients. D’Angelica et al. also found no significant difference in postoperative complications in patients who were treated with bevacizumab an average of 6.9 weeks before surgery or 7.4 weeks after surgery when compared with a group of matched historical controls (D’Angelica et al., 2007). Currently, the precise timing to initiate bevacizumab treatment before or after surgery to avoid postoperative wound-healing complications is not clear (Nordlinger et al., 2009), but an interval of 5 to 8 weeks has been suggested (Gruenberger et al., 2008; Ellis et al., 2005; Reddy et al., 2008).

6 Chemotherapy for mCRC

Resection of the primary tumor significantly increased the hospital stay and delayed the initiation of chemotherapy; however, there was no evidence to suggest that this delay was associated with reduced response rates leading to curative resection or reduced survival. Recently, it was reported that the growth rate of liver metastases in patients in whom the primary colorectal tumor had been resected was significantly higher than the growth rate of liver metastases in patients in whom the primary tumor was still in situ (Peeters et al., 2004; Simpson-Herren et al., 1976). In addition, immunohistochemical analysis revealed an increased proliferation rate and increased vessel density in the metastases in the absence of the primary tumor. These data suggest that outgrowth of metastatic disease may be partially controlled by the primary tumor (Peeters et al., 2006). Patients may therefore die if they are not able to initiate chemotherapy because of the rapid postoperative progression of a metastatic tumor (Makino et al., 2006; Tajima et al., 2006). We reported a case involving an early initiation of chemotherapy in a patient who had undergone a right hemicolecctomy for multiple synchronous liver metastases (Yoshida et al., 2011). He survived for 22 months despite large liver metastases. We began the prospective study to confirm the feasibility of an early initiation of chemotherapy after surgery (Trial registration: UMIN000004361). To the best of our knowledge, this was the first pilot study to determine the feasibility of an early initiation to chemotherapy after resection of a primary colorectal cancer with distant metastases, and it was undertaken only in a small cohort of well-selected patients. Five patients were enrolled. They received XELOX therapy (130 mg/m2 of oxaliplatin on day 1 plus 1,000 mg/m2 of capecitabine twice daily on days 1 – 14) on the 7th postoperative day and XELOX+bevacizumab (7.5 mg/kg of bevacizumab on day 1) after the 2nd cycle of chemotherapy. The procedures included right hemicolecctomy in 1 patient, sigmoidectomy in 2 patients, high anterior resection in 1 patient, and Hartmann procedure in 1 patient. All patients started chemotherapy on postoperative day 7. The median number of cycles of chemotherapy was 11 (8 – 22). No postoperative complications were observed. The tumor reduction rate was 44.3% (32.0 – 66.6%). Progression-free survival was 10.3 months. An early initiation of chemotherapy after surgery may be safe and may improve the prognosis of colorectal cancer patients with synchronous metastases. These findings suggest the potential for changes in the suggested time of initiation of chemotherapy after surgery in the
future. We have already begun a new phase II trial to confirm the effects of the early initiation of chemotherapy after surgery.

Enhanced recovery after surgery (ERAS) protocols aim to reduce the surgical stress response and optimize recovery to reduce the length of hospital stays (Lassen et al., 2009). All ERAS parameters have been shown to improve patient outcome individually. The development of ERAS enabled an early start to chemotherapy after surgery. An early initiation of chemotherapy after surgery may therefore prevent tumor growth. Resection of colorectal tumors with severe stenosis and bleeding is the first treatment step in preventing complications related to colorectal tumors. The European multicenter COlon cancer Laparoscopic or Open Resection (COLOR) trial assessed the short-term and long-term outcomes after laparoscopic surgery or open surgery for colon cancer (Veldkamp et al., 2005; Buunen et al., 2009). Allaix et al. reported a higher percentage of patients submitted to adjuvant chemotherapy within 8 weeks in laparoscopic surgery group, due to a shorter hospital stay and a quicker return to preoperative performance status (Allaix et al., 2012). The opportunity of an early onset of adjuvant chemotherapy could represent a further theoretical advantage of minimally invasive surgery in metastatic CRC patients compared with open surgery. An earlier administration will be made possible using this minimally invasive surgery for the treatment of advanced colon cancer. This early chemotherapy may extend the prognosis for patients who undergo laparoscopic surgery for colon cancer.

Recently, the use of the self-expandable metal stent (SEMS) as a nonsurgical alternative for relief of obstructing colorectal cancer has increased. The effects of chemotherapy after SEMS placement are controversial. One study was closed prematurely because of chemotherapy-induced colonic perforation in 54% (6/11) of patients (van Hooft et al., 2008). Another report found, in contrast, that complications including perforation and stent migration were not associated with additional chemotherapy (Fernandez-Esparra et al., 2010). However, these results were limited by the small numbers of patients included. Yoon et al. reported that 126 patients who achieved immediate clinical success from palliative SEM-placement, cumulative long-term clinical failure occurred more frequently in patients who did not receive post-stent chemotherapy than in those who received chemotherapy (Yoon et al., 2011). In other words, receiving additional chemotherapy after palliative stenting contributed to long-term clinical success. This may have been caused by the effects of tumor shrinkage from chemotherapy (Im et al., 2008). This hypothesis was indirectly supported by the subanalysis. Although there was no difference in the long-term clinical failure rate according to cancer subtype, differentiated cancers (well-differentiated and moderately differentiated adenocarcinoma) had a lower long-term clinical failure rate than undifferentiated cancers (poorly differentiated adenocarcinoma, signet-ring cell carcinoma, etc), which are generally regarded as rapidly progressive and less chemotherapy responsive tumors.

7 Discussion

The National Comprehensive Cancer Network currently recommends that patients with metastatic colorectal cancer undergo surgical intervention if they have a bowel obstruction, an impending obstruction, or metastases that are potentially resectable. Complications from the primary lesion are uncommon in these circumstances, and the removal of the lesion delays the initiation of systemic chemotherapy. The precise timing for starting treatment with chemotherapeutic agents prior to and/or after surgery in order to avoid postoperative complications is not clear, but an at least 4-week interval has been suggested. In most clinical trials, patients who had undergone an operation within 4 weeks were excluded. Resection of the pri-
mary tumor significantly increased the hospital stay and delayed the initiation of chemotherapy; however, there was no evidence to suggest that this delay was associated with reduced response rates leading to curative resection or reduced survival. However, there is a chance that patients may die if they are not able to start chemotherapy because of the rapid postoperative progression of a metastatic tumor.

We have carried out the prospective study to confirm the feasibility of an early start of chemotherapy after surgery, and a phase II trial should be performed to confirm the safety and effects of the early start of chemotherapy after surgery.

8 Conclusion

An early start of chemotherapy after surgery is feasible and safe. These findings suggest possible changes in the start time of chemotherapy after surgery in the future. We have already started a new phase II trial to confirm the effects of the early start of chemotherapy after surgery.

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