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Original Article

Neoadjuvant with Folfox6 in Initially Unresectable Liver Metastasis in Colorectal Cancer

ผลการรักษามะเร็งลำไส้ใหญ่และทวารหนักระยะแพร่กระจายไปยังตับด้วยการให้ยาเคมีบำบัดสูตร Folfox6 ก่อนการผ่าตัด

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ABSTRACT

Background : Colorectal cancer is one of the commonest solid tumors. The liver is the commonest site of distant metastasis. Hepatic resection is the only form of treatment that offers a chance of long-term survival. Recently Folfox regimen (5 FU, leucoverin and oxaliplatin) showed benefit in stage 4 colorectal cancers and was recommended to be one of standard regimen.

Patients and methods : From January 2005 to December 2006, 63 patients with unresectable liver metastases from colorectal cancer were treated with chemotherapy, Folfox regimen {Oxaliplatin 85 mg/m^2, Leucoverin 200 mg/m^2 5 FU 400 mg/m^2 IV bolus and 5 FU 1200 mg/m^2/day x 2 days continuous infusion and repeat every 2 weeks (Folfox6)} and measured response. Hepatic resection was reconsidered when technically possible.

Results : Sixty three patients who received Folfox6 could convert to resectable tumors in 12 (19%) patients and underwent hepatectomy. In hepatectomy cases, 3 (25% underwent a minor hepatectomy and 9 (75%) had a major hepatectomy. Associated lung resections were done in 2 cases. Complication rate was 33.3%. Hepatic recurrence was observed in 1 patient (8.3%) after a mean follow-up of 12 months. At 1 year median follow up time, 11 patients survived without disease.

Conclusions : Neoadjuvant with Folfox6 improved hepatic resection in previously unresectable liver metastases from colorectal cancer. An aggressive surgical approach in these patients may provide a reasonable hope of long-term survival.

บทคัดย่อ

มะเร็งลำไส้ใหญ่และทวารหนักเป็นมะเร็งที่พบบ่อยและมักแพร่กระจายไปยังตับ การผ่าตัดเอาก้อนออกเป็นวิธีการรักษาเดียวที่ได้ผลในระยะยาว ปัจจุบันการให้ยาเคมีบำบัดสูตร Folfox ได้ผลการรักษาที่ดีและใช้เป็นมาตรฐาน

ตั้งแต่เดือนกรกฎาคม 2548 ถึง เดือนธันวาคม 2549 ผู้ป่วยมะเร็งลำไส้ใหญ่และทวารหนักที่มีการแพร่กระจายไปยังตับและผ่าตัดไม่ได้ 63 ราย คน ได้รับการรักษาด้วยยาเคมีบำบัดสูตร Folfox 6 และวัดผลการรักษา มีผู้ป่วย 12 ราย (19%) สามารถนำไปผ่าตัดตับออกได้ โดย 3 ราย (25%) เป็นการตัดตับจำนวนไม่มาก และ 9 ราย (75%) เป็นการตัดตับตั้งแต่ 3 ส่วนขึ้นไป พบมีการกลับเป็นซ้ำ 1 ราย หลังจากการเฝ้าติดตาม เป็นเวลา 12 เดือน อีก 11 ราย ไม่พบการกลับเป็นซ้ำ

การให้ยาเคมีบำบัดสูตร Folfox6 ก่อนการผ่าตัด ในผู้ป่วยมะเร็งลำไส้ใหญ่และทวารหนักที่มีการแพร่กระจายไปยังตับและผ่าตัดไม่ได้ สามารถช่วยเปลี่ยนระยะและทำให้สามารถผ่าตัดได้และช่วยเพิ่มโอกาสมีชีวิตรอดในระยะยาว

Introduction

Colorectal cancer is one of the commonest solid tumors in human beings and is responsible for approximately 10 percent of the cancer death in Western world[3-5]. Approximately half of all patients with colorectal cancer present at some stage with hepatic metastases[6,7]. The liver is the commonest site of distant metastasis in this disease and nearly half of the patients with colorectal cancer ultimately develop liver involved during the course of their diseases[8]. Hepatic resection currently is the only form of treatment that offers a chance of long-term survival, with rates ranging from 25% to 39% reported in the literature[9-13]. However, using current indications for surgery, it is estimated that a curative operation can be performed in only 10% of all patients with colorectal metastases to the liver[6-7]. In the remaining patients-the majority-the prognosis is poor and symptomatic treatment or palliative chemotherapy are the only options available. Systemic chemotherapy using conventional cytotoxic agents, mainly 5-fluorouracil, is effective in some cases, but long-term survival is uniformly poor[14]. Recently Folfox regimen (5 FU, leucoverin and oxaliplatin) show benefit in stage 4 colorectal cancers and was recommended to be one of standard regimen[15]. In this study, a group of patients with liver metastases who initially were unable to do primary surgical resection responded to chemotherapy to the point that hepatectomy was reconsidered and performed. This study presents the results of this combined approach.

Patients and method

From January 2005 to December 2006, 63 patients with unresectable liver metastases from colorectal cancer were treated in Nakhonpathom hospital. In all patients, a complete clinical, laboratory, and radiologic work-up was undertaken to detect evidence of local and disseminated disease. All patients in this group were treated with systemic chemotherapy, according to the description that follows. All were periodically reviewed with regard to modification of the criteria contraindicating primary resection. All of these patients received Oxaliplatin 85 mg/m^2 IV over 2 hours, day1 then Leucoverin

200 mg/m^2 IV over 2 hours day1 then followed by 5 FU 400 mg/m^2 IV bolus day 1, then 5 FU 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) continuous infusion and repeat every 2 weeks (Folfox6)[16-17]

Hepatic resection was reconsidered periodically, along with the objective response to chemotherapy, and was attempted when technically possible and when potentially curative. To optimize the chances of curative resection, our policy was to perform the hepatectomy when the reduction in tumor size on repeated computed tomography. When liver metastases were associated with pulmonary metastases and both were resectable, our policy was first to perform the liver resection and then, after two to three courses of chemotherapy, the pulmonary resection. This approach seems logical because it first removes the potential liver reservoir of neoplastic cells, which can migrate at surgery. A complete examination of the liver was performed by palpation and intraoperative ultrasonography to confirm the number and size of metastases, to define their relationship with intrahepatic vascular structures, and to look for occult liver metastases.

Results

From January 2005 to December 2006, 63 patients with unresectable liver metastases from colorectal cancer were treated in Nakhonpathom hospital. All patients in this group were treated with systemic chemotherapy, Folfox regimen. Characteristic of the patients as describe in Table 1

Table 1 Patient's characteristic

	Number (%)
Age, years	
Median (range)	54 (31-72)
Karnofsky performance status	
Median (range)	80 (70-90)
Gender	
Male	33 (52.4)
Female	30 (47.6)
Tumor Anatomic location	
Right lobe	20 (50.0)
Left lobe	10 (25.0)
Both lobe	10 (25.0)
Largest tumor diameter	
No. of metastasis (range)	4 (2-6)
No. of segment involve (range)	3 92-5)
No. of chemotherapy (cycles)	12 (6-24)

Of the 63 patients, neoadjuvant chemotherapy with Folfox6 can convert unresectable tumors to resectable tumors in 12 (19%) patients and underwent hepatectomy. In hepatectomy cases, 3 (25% underwent a minor hepatectomy (less than 3 segments) and 9 (75%) had a major hepatectomy (> 3 segments). No difference in the extent of resection was noted between groups. The mean number of blood units transfused during the operation was 4.2 (range, 3-8 units) in the group of patients with large tumors, 2.5 (range, 0-6 units) in the group with small tumors. Associated lung resections were done in 2 cases. Complication rate is 33.3% (details as in table 2). Hepatic recurrence was observed in 1 patient (8.3%) after a mean follow-up of 12 months. At 1 year median follow up time, 11 patients survived without disease.

Table 2 Results of treatment

	Number (%)
Conversion to resectable tumors	12 (19)
Minor liver resection (< 3 segments)	3(25)
Major liver resection (> 3 segments)	9 (75)
Post operative mortality	0
Survived patients at 1 year follow up	11 (91.7)
Associated procedure (lung resection)	2 (16.7)
Complications	4 (33.3)
Intra-abdominal collection (no surgery)	2 (16.7)
reoperation for intra-abdominal bleeding	1 (8.3)
transient biliary leaks	1 (8.3)

Discussions

This study presents the results of potentially curative secondary hepatectomy on 12 patients whose primarily unresectable colorectal liver metastases were downstaged by chemotherapy. The fact that patients with liver metastases initially considered unsuitable for radical surgery can undergo potentially curative surgery after chemotherapy is a recent concept in the management of these patients. To the present day, the criteria for liver resection are changed to preservation of at least 1 of 3 hepatic vein, get 1 cm margin if possible, can complete resection of all tumors and leave remnant liver tissue > 30%[18].

Among the patients with colorectal liver metastases, resection is the only treatment offering a chance of long term survival[9-13]. Unfortunately, surgery will not be possible in up to 90% of patients, either because of extrahepatic disease or because the hepatic lesions are not amenable to excision. Furthermore, it is uncommon that a patient whose disease initially is considered beyond operative treatment will be offered a second chance for resection[19]. Survival of patients with unresectable hepatic metastases from colorectal cancer is poor, ranging from 3 to 6 months when both lobes of the liver are involved[20,21]. Expectant symptomatic treatment and palliative chemotherapy are the most common modalities of treatment. Systemic chemotherapy is used most frequently. The standard drug is 5-fluorouracil, with response rates reported between 15% and 25%.[12,22] More recently, studies with 5-fluorouracil, Leucoverin and Oxaliplatin have demonstrated 1st line clinical responses in approximately 40% of patients.[23,24] However, the benefit is small and median survival does not exceed 11 to 19.5 months. [24-27]

This study used Folfox6 that is highly effective regimen for downsizing tumors. A high response rate was observed, which allowed a subsequent resection in 12 of 63 patients initially considered unresectable by our surgical team (19%).

Surgical treatment of these patients requires all of liver surgery techniques. Intraoperative ultrasound was an indispensable tool for a complete diagnosis of the tumoral disease and for planning the adapted surgical procedure and new instrument for reduced bleeding when resection such as ultrasonic dissector and plasma kinetic clamp. The objective of liver resection was to remove all tumor tissue, with a margin of security of at least 1 cm. However, in cases in which the tumors arrived in contact with the main vessels, the margins had to be more limited. In multinodular tumors, the margins also were limited by the number of nodules and their proximity to main vascular structures. Livers submitted to prolonged chemotherapy often were more fragile and hemorrhagic than healthy livers from steatohepatitis or sinusoidal dilatation (peliosis).[28] This attitude, associated with chemotherapy, allowed disease-free survival in more than one third of patients (36%). It may be argued that this proportion represents a minority of patients with regard to the aggressiveness of our strategy. However, these results are comparable with those observed after conventional liver resection of colorectal metastases.[9-13] The criticism could be made that our policy of treating with chemotherapy all patients with unresectable colorectal metastases casts too wide a net for the small number of patients in whom downstaging occurs and who can benefit from secondary resections. Currently, it is impossible to predict which individual will respond and which will not, and further work is needed in this direction. It also has to be added that systemic chemotherapy is accepted as the standard treatment in our country for patients with unresectable colorectal liver metastases, whether they are considered for secondary surgery or not and most patients are receiving it regardless of whether secondary resections are considered. Further effort also is needed to obtain still more effective chemotherapeutic protocols, such as combination regimen with targetted therapy[29,30] to increase the

proportion of patients who can be resected secondarily and to lower the high incidence of recurrence seen after surgery.

Conclusion

The performance of hepatic resections after tumor response to chemotherapy improved in selected patients the poor prognosis of previously unresectable liver metastases from colorectal cancer. An aggressive surgical approach in these patients may provide a reasonable hope of long-term survival.

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