Original Article

Computed Tomography in the Postoperative Surveillance of Stage III Colorectal Cancers Receiving Adjuvant Chemotherapy

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Key Words
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Purpose. Colorectal cancer (CRC) is the most common malignancy in Taiwan. Approximately 30-50% of CRC patients receiving radical resection will eventually develop postoperative relapse. Surveillance for early detection of postoperative relapse is the ideal goal, and computed tomography (CT) scan is the crucial tool for such surveillance for stage III CRC patients administrated with adjuvant chemotherapy; however, the routine role of CT scan in the post-chemotherapeutic surveillance in local recurrence or distant metastasis of these patients in the clinical practice remains largely unknown.

Methods. From January 2008 to February 2011, a retrospective analysis of 115 stage III CRC patients undergoing primary lesion resection following by adjuvant chemotherapy was investigated. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CT scan for the diagnosis of postoperative local recurrence and distant metastasis were analyzed.

Results. There were no significant differences between colon and rectal cancer patients in age (p = 0.798), gender (p = 0.242), tumor size (p = 0.288), tumor depth (p = 0.059), and lymph node metastasis (p = 0.557). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CT scan for colon cancer or rectal cancer patients in the diagnosis of distant metastasis are similar. However, the sensitivity of CT scan in the diagnosis of local recurrence in colon cancer (22.2%) and rectal cancer (50%) was relatively low.

Conclusion. Our study showed that the sensitivity for diagnosis of local recurrence in colon and rectal cancer patients is prominently lower than that of distant metastasis by CT scan. Therefore, more precise image studies in the surveillance may be mandatory to improve accurate detection of local recurrence for CRC patients following adjuvant chemotherapy.

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Colorectal cancer (CRC) is the most common malignancy in Taiwan. Despite optimal primary treatment, with adequate surgery with or without adjuvant chemotherapy, approximately 30-50% of patients will relapse and die of their disease. In the past, there was insufficient evidence that post-operative regular outpatient department follow-up could significantly improve overall survival. The improvement in overall survival has been attributed to earlier detection of recurrent disease and in particular, to a higher rate of detection of isolated locoregional relapses. Recently, four systemic revisions of ESMO clinical recommendations have proven that overall survival gain was 7-13% for patients undergoing intensive surveillance compared with those with minimal or no follow-up.[1] Detection of early relapse of colon cancer is the ideal goal of surveillance. Carcinoembryonic antigen (CEA), abdominal and chest computed tomography (CT), positron emission tomography (PET), and colonoscopy are usually used in clinical practice for follow-up. CEA determination is recommended every 3-6 months for 2 years according to the National Comprehensive Cancer Network (NCCN) guideline 2012 Ver. 2.[2] It is estimated that in 90% of patients with serum CEA level elevation after surgery, local recurrence or distant metastasis is indicated.[3] Serum CEA elevation could be detected 1.5-6 months before positive finding of other examinations. But the false-positive rate of CEA elevation is 7%-16% and the false-negative rate is 40%.[1] Other image examinations should be combined to improve the accuracy of detecting local recurrence or distant metastasis. PET, PET-CT, MRI, and CT can be used for CRC patients with elevated CEA levels in the detection of local recurrence or distant metastasis in surveillance. The PET and PET-CT scan are both metabolic techniques and more precise tools to detect malignant lesions because malignant lesions exhibit higher glucose metabolism and higher uptake of FDG. The sensitivity of PET or PET-CT is higher than CT in detection of cancer relapse.[4] It is not cost-effective in surveillance by PET or PET-CT scan despite the CT scan having lowest diagnostic performance and economic benefits.

In detection of hepatic metastasis of CRC patients, it has been proven that CT scan is more useful than liver function test or CEA level.[5] The post-operative CRC patients with regular liver imaging had 25% lower mortality rate compared with those without regular liver imaging.[6] In addition, Chau et al. pointed out that the CT-detected group had better survival time (13.8 months) than the symptomatic group in surveillance.[7]

FOLFOX4 regimen (oxaliplatin/5-fluorouracil/leucovorin) is standard adjuvant chemotherapy in stage III colon cancer patients.[8] The role of CT scan in the postoperative surveillance for stage CRC patients treated with FOLFOX4 regimen is not clear. The aim of this study is to assess diagnostic accuracy of contrast-enhanced computed tomography (CT) scan in the detection of the local recurrence or distant metastasis for postoperative surveillance in colorectal cancer patients following adjuvant chemotherapy.

Materials and Methods

Patients

Between January 2008 and February 2011, a retrospective analysis of UICC stage III 115 patients from Kaohsiung Medical University Hospital with colorectal cancer (CRC) undergoing primary tumor resection following by FOLFOX4 adjuvant chemotherapy was investigated. FOLFOX-4 was conducted comprising oxaliplatin 85 mg/m^2 as a two-hour infusion on day 1, LV 200 mg/m^2 as a two-hour infusion concurrently with oxaliplatin on day 1, followed by a bolus of 5-FU 400 mg/m^2 then and continuous infusion of 5-FU 600 mg/m^2 over 22-hours (days 1 and 2), and was repeated every two weeks in the presence of an absolute neutrophil count ≥ 1500/μl and platelet count ≥ 100000/μl, and recovery of any extra-haematological toxicity; otherwise, treatment was postponed for one or two weeks until recovery. Also, the chemotherapy was continued until the disease progressed or unacceptable toxicities developed or the patient refused further treatment with FOLFOX4. Postoperative surveillance consisted of medical history, physical examination, and laboratory studies including serum carcinoembryonic antigen (CEA) levels every 3 months, abdominal ultrasonography was performed every 6 months, and chest radiography and

total colonoscopy were performed once a year. Abdominal- or chest-computed tomography (CT) scan was scheduled every 6-cycle interval of FOLFOX4 chemotherapy. Patients were regularly followed up at 3-monthly intervals for 2 years and 6-monthly intervals thereafter. For the uniform quality of computed tomography reading, all computed tomography image of 115 patients are read by the same senior radiologist (Dr. Chau-Yun Chen) in CRC multi-disciplinary team of Kaohsiung Medical University Hospital.

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences version 17.0 software (SPSS Inc., Chicago, IL, USA). The student *t*-test was used to compare age between colon and rectal cancer patients. Chi-squared test was used to compare gender, tumor size, tumor depth, and lymph node metastasis in colon and rectal cancer patients. It was considered statistically significant if the p value < 0.05. The sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy of CT scan in local recurrence and distant metastasis were evaluated.

Results

Patient characteristics

The characteristics of the 115 UICC stage III colorectal cancer patients are summarized in Table 1, and there were 90 colon cancer patients and 25 rectal cancer patients. The median age was 63 years in colon cancer patients (range from 30 to 84) and 67 years in rectal cancer patients (range from 34 to 81). The median follow-up time is 34 months (range from 14 to 51). Among 90 colon cancer patients, there were 42 patients with tumor size longer than 5 cm and 48 patients with tumor size smaller than 5 cm. In tumor depth, 6 patients were T1-T2 and 84 patients were T3-T4. In lymph node metastasis, 63 patients were N1 and 27 patients were N2. Among 25 colon cancer patients, there were 7 patients of tumor size longer than 5 cm and 18 patients of tumor size smaller than 5 cm. In tumor depth, 5 patients were T1-T2 and 20 patients were T3-T4. In lymph node metastasis, 19 patients were N1 and 6 patients were N2. There were no significant statistically differences between colon and rectal cancer patients in age (p = 0.798), gender (p = 0.242), tumor size (p = 0.288), tumor depth (p = 0.059), and lymph node metastasis (p = 0.557). Computed tomography was used to evaluate the local recurrence and distant metastases in colon and rectal cancer patients (Table 2), which was compared to pathology or positron emission tomography (PET) scan if the pathology sample was not available. There were 36 and 10 patients with local recurrence in colon and rectal cancer patients respectively by CT diagnosis, and 8 (22.2%) and 5 (50%) patients were proven by pathology or consistent with PET scan in colon and rectal cancer patients respectively. There were 22 and 9 patients with distant metastasis in colon and rectal cancer patients respectively by CT diagnosis, and 18 (81.8%) and 8 (88.9%) patients were proven by pathology or consistent with PET scan in colon and rectal cancer patients respectively. Twenty-two patients with distant metastases were diagnosed by CT scan as colon cancer patients.

Table 3 summarizes the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CT scan in evaluating the local recurrence or distant metastasis in colon and rectal cancer

Table 1. Characteristics of 115 UICC stage III colorectal cancer patients

	Colon cancer N = 90	Rectal cancer N = 25	*p*
Age (years)			0.798
Median (range)	63 (30-84)	67 (34-81)	
Gender			0.242
Male	48	17	
Female	42	8	
Tumor size			0.288
≧ 5 cm	42	7	
< 5 cm	48	18	
Tumor depth			
T1+T2	6	5	0.059
T3+T4	84	20	
Lymph node metastasis			
N1	63	19	0.557
N2	27	6	

Table 2. Abdominal computed tomography or pathology/PET scan in evaluating the local recurrence and distant metastases in colon and rectal cancer patients

	Colon cancer N = 90		Rectal cancer N = 25	
Site of metastasis	CT diagnosis	Pathology or PET scan diagnosis	CT diagnosis	Pathology or PET scan diagnosis
Local recurrence	36	8	10	5
Distant metastasis	22	18	9	8
Liver only	7	6	4	3
Lung only	1	1	1	1
Bone only	1	1	1	1
Ovary only	1	1	0	0
Spleen only	1	0	0	0
Multiple metastases	11	9	3	3

CT: computed tomography; PET: positron emission tomography.

Table 3. Sensitivity, specificity and positive and negative predictive value of abdominal computed tomography in evaluating the local recurrence or distant metastasis in colon and rectal cancer patients

	Pathology or PET scan diagnosis			
	Colon cancer		Rectal cancer	
CT diagnosis	Local recurrence	Distant metastasis	Local recurrence	Distant metastasis
Sensitivity	8/36 (22.2%)	18/22 (81.8%)	5/10 (50%)	8/9 (88.8%)
Specificity	51/54 (94.4%)	65/68 (95.6%)	14/15 (93.3%)	16/16 (100%)
PPV	8/11 (72.7%)	18/21 (85.7%)	5/6 (83.3%)	8/8 (100%)
NPV	51/79 (64.6%)	65/69 (94.2%)	14/19 (73.6%)	16/17 (94.1%)
Accuracy	59/90 (65.6%)	83/90 (92.2%)	19/25 (76%)	24/25 (96%)

CT: computed tomography; PET: positron emission tomography; PPV: positive predictive value; NPV: negative predictive value.

patients respectively. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of abdominal CT for colon cancer with distant metastasis were 81.8%, 95.6%, 85.7%, 94.2%, and 92.2%, which were similar to the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CT scan for rectal cancer with distant metastasis, 88.8%, 100%, 100%, 94.1%, and 96% respectively.

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CT for colon cancer with local recurrence were 22.2%, 94.4%, 72.7%, 64.6%, and 65.6%. Moreover, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CT for rectal cancer with local recurrence are 50.0%, 93.3%, 83.3%, 73.6%, and 76%. The accurate detection rate was relatively low in local recurrence in colon and rectal cancer patients when compared to the accurate detection rate in distant metastasis in colon and rectal cancer patients.

Discussion

Earlier detection of relapse is the main purpose in surveillance after surgery and adjuvant chemotherapy has been proven to improve overall survival. Renehan et al. pointed out that earlier detection of recurrences can lead to substantial reduction (about 9%-13%) in mortality of stage III CRC patients with adjuvant chemotherapy.[9] In addition, an improvement of 7% in five-year overall survival was also demonstrated.[10] Based on the recommendations of the American Society of Clinical Oncology, it is recommended asymptomatic recurrences of CRC after surgery be detected by measurement of serum carcinoembryonic antigen (CEA).[11] The recurrences were eventually confirmed in 90% of CRC patients with elevated serum CEA levels after operation.[10] According to the National

Comprehensive Cancer Network (NCCN) guidelines 2012 Ver. 2, history, physical examination, and CEA determination are advised to be evaluated every 3 months for at least 2 years and every 6 months for a total of 5 years. CT scan of abdomen and pelvis is annually for 3 years. Colonoscopy is performed at first year, then as clinically indicated.

In the current study, among 34 colon cancer patients with elevated CEA, 26 (76.5%) patients were subsequently proven with local recurrence or distant metastases. However, among 58 patients with abnormal CT finding, only 26 (44.8%) patients were eventually proven with local recurrence or distant metastases. It seems that CEA measurement is more sensitive than CT scan in post-chemotherapeutic surveillance. In fact, CEA measurement and CT scan are both important tools in clinical surveillance according to NCCN guidelines.

Besides, how to distinguish local recurrence of CRC patients from previous surgery-related or radiation-related fibrotic mass with CT images is difficult in clinical practice.[12] In our investigation, the sensitivity and specificity for differentiating local recurrence from fibrotic mass with CT images among patients with colon cancer were 22.2% and 94.4% respectively. The sensitivity and specificity for differentiating local recurrence from fibrotic mass with CT images among patients with rectal cancer were 50% and 93.3% respectively. The sensitivity of local recurrence by CT scan in colon and rectal cancer patients is relatively lower than sensitivity of distant metastasis. It suggests that CT scan seems to be a more reliable tool for detection of distant metastasis than in local recurrences for stage III CRC patients administrated with adjuvant chemotherapy. Consequently, other diagnostic tools to accurately identify local recurrences is necessary for these patients.

In recent decades, the functional data of fluorine 18 (18F) fluorodeoxyglucose (FDG) PET scan have an important role to distinguish recurrent tumoral masses in patients with CRC after surgery from non-recurrent masses.[13-15] Even-Sapir et al. revealed that among 62 patients with CRC after surgery evaluated by abdominal CT scan, 30 (48%) patients were abnormal by CT scan but only 7 (23%) patients were finally proven to be consistent. This result is similar to our current study, where 46/115 (40%) patients were abnormal by CT scan but only 13 (28.3%) patients were consistent. Among 81 patients with increased 18F FDG uptake by PET scan, sensitivity and specificity for differentiating malignant from benign tumors were 82% and 65% respectively. When PET is combined with CT scan to distinguish recurrent masses and non-recurrent masses, the sensitivity and specificity are prominently increased to 100% and 96% respectively.[15] The PET-CT is not the same as pathological proven metastases. In our investigation the most metastases are proven pathologically with specimen from surgery or colonoscopy. However a few part of metastases are proven by PET-CT because of the patient's personal reason or difficulties in retroperitoneal and pre-sacral specimen. Those are relatively rare. Though the PET scan is more accurate for detection of recurrence compared with CT only, it is not recommended to be used routinely for initial diagnosis of CRC.

Conclusion

How to detect the early relapse of CRC patients administrated with adjuvant chemotherapy remains a challenge to clinicians. The relatively low accuracy of routine CT scan in the detection of local recurrence in CRC patients following adjuvant chemotherapy needs to be justified. Particularly, the actual role of PET scan for the surveillance of these patients needs to be explored in further studies.

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原　著

電腦斷層用於接受手術與輔助性化療後之第三期大腸癌病人的追蹤

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目的　大腸直腸癌在台灣是最常見的惡性腫瘤。大腸直腸癌的病人即使接受完整的手術治療，還是有 30~50% 會復發。早期發現腫瘤復發是術後追蹤的首要目標。在第三期大腸直腸癌手術及輔助性治療後追蹤工具以電腦斷層為主。然而電腦斷層攝影在臨床常規檢查的診斷正確性仍然是未明。

方法　從 2008 年 1 月至 2011 年二月，我們統計並分析了 115 個接受過手術併輔助性治療的第三期大腸直腸癌病人，這些病人皆是高醫的病人。就電腦斷層對診斷大腸直腸癌術後局部復發和遠端轉移的敏感性，特異性，陽性預測值，陰性預測值，和正確度進行分析。

結果　大腸癌及直腸癌的病人中，在年齡 ($p = 0.798$)，性別 ($p = 0.242$)，腫瘤大小 ($p = 0.288$)，腫瘤侵犯深度 ($p = 0.059$)，和淋巴結轉移 ($p = 0.557$) 統計上沒有顯著的差異。在電腦斷層對遠端轉移的敏感性，特異性，陽性預測值，陰性預測值，和正確度方面，大腸癌和直腸癌是相似的。然而，在電腦斷層對診斷局部復發的敏感性，大腸癌 (22.2%) 相對比直腸癌 (50%) 較低。大腸癌及直腸癌的病人中，在年齡 ($p = 0.798$)，性別 ($p = 0.242$)，腫瘤大小 ($p = 0.288$)，腫瘤侵犯深度 ($p = 0.059$)，和淋巴結轉移 ($p = 0.557$) 統計上沒有顯著的差異。在電腦斷層對遠端轉移的敏感性，特異性，陽性預測值，陰性預測值，和正確度方面，大腸癌和直腸癌是相似的。然而，在電腦斷層對診斷局部復發的敏感性，大腸癌 (22.2%) 相對比直腸癌 (50%) 較低。

結論　我們的研究指出在大腸癌和直腸癌的病人，電腦斷層在診斷局部復發的敏感性明顯較低於診斷遠端轉移的敏感性。所以，對於接受輔助性治療的大腸直腸癌病人，應該安排更精確的影像工具去改善偵測局部復發的正確度。

關鍵詞　電腦斷層、術後追蹤、第三期大腸直腸癌。