Is Routine Chest and Abdominopelvic CT Necessary for all Postoperative Gastric Cancer Patients?

<Original Article>

Is Routine Chest and Abdominopelvic CT Necessary for all Postoperative Gastric Cancer Patients?

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ABSTRACT

Background: The aim of this study was to clarify the necessity of routine chest CT in the follow-up of postoperative gastric cancer (GC) and the optimal CT interval based on risk determined by pathological stage (PS; pT and pN) to minimize radiation exposure to patients.

Method: The subjects were 361 postoperative patients with primary GC. We retrospectively evaluated sites of recurrence, time to recurrence revealed on chest and abdominopelvic CT, and PS.

Results: Forty-two patients experienced recurrences. The pN factor was more strongly associated with thoracic metastasis than pT factor in patients with N0-1 ($n = 278$) versus those with N2-3 ($n = 83$) ($p < 0.05$) and in those with T1-2 versus those with T3-4 ($p = 0.48$). None of the 278 patients with pN0-1 had chest metastasis. Among the 83 patients with pN2-3, only abdominal lymph node recurrence was significantly associated with thoracic metastasis. Recurrences were detected within two years after resection in 38 patients (90 %) regardless of PS.

Conclusion: Abdominal lymph node recurrence as well as pN factor were significantly associated with thoracic metastases and actually none of patients with pN0-1 had chest metastases. These facts implied limited role of routine chest CT for those patients.

INTRODUCTION

Gastric cancer is the fifth most common cancer worldwide, and was the fourth leading cause of cancer deaths in 2020 [1]. Locally advanced gastric cancer is treated by curative radical resection, but a significant proportion of patients experience recurrence, which almost always leads to a fatal event. Although some retrospective studies have investigated postoperative recurrence of gastric cancer, these studies do not provide sufficiently convincing evidence to inform sur-

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veillance strategies for postoperative gastric cancer. The National Comprehensive Cancer Network (NCCN) guidelines [2] also note that surveillance strategies after curative-intent resection for gastric cancer remain controversial. On the other hand, some retrospective studies [3–5] have concluded that computed tomography (CT) is one of the best modalities for detecting recurrence of gastric cancer. The approach at our hospital has been to routinely perform follow-up chest and abdominopelvic CT for almost all patients after gastric cancer surgery. However, there is a need to investigate how to tailor the follow-up CT interval and scan range to each postoperative patient to minimize radiation exposure. Therefore, we analyzed a large series of chest and abdominopelvic follow-up CT scans and the clinical characteristics of postoperative gastric cancer patients to establish appropriate use of CT based on risk determined by pathological tumor grade (pT) and lymph node grade (pN), sites of recurrence and their metastatic pattern on CT, as well as the number of CT scans, and to determine whether tumor markers and esophagogastroduodenoscopy (EGD) can be reliable indicators of recurrence as well as warrant use of CT.

METHODS

Patients

This was a retrospective study conducted with the approval of our hospital's institutional review board, with the requirement to obtain informed consent waived. We reviewed the records of 1634 patients recorded in the tumor registry at Osaka Medical and Pharmaceutical University Hospital from February 2014 to December 2019 to retrieve data on gastric cancer patients who underwent radical surgery ($n = 751$). The remaining registry consisted of patients who received endoscopic submucosal dissection (ESD) and chemotherapy alone. Patients were excluded if they had multiple primary cancers including gastroesophageal junction tumors ($n = 329$), received neoadjuvant chemotherapy ($n = 30$), never underwent even one CT scan ($n = 7$), or their follow-up was interrupted ($n = 24$). Consequently, 361 patients were included in the analysis.

All patients were diagnosed with gastric cancer by EGD with biopsy, and clinical staging was performed with chest and abdominopelvic CT before radical gastrectomy in almost all patients. This group included some patients with post-ESD recurrence. The pathological stage was determined by pathologists at our hospital. Pathological stage (pT and pN) and primary tumor site were coded using the Union for International Cancer Control (UICC) TNM classification. Postoperative chemotherapy was performed depending on postoperative results, in line with the Gastric Cancer Treatment Guidelines published by the Japanese Gastric Cancer Association. For patients with stage I disease, postoperative follow-up consisted of physical examination and laboratory tests including tumor markers every 6 months, and chest and abdominopelvic CT every year. For stage II and III, follow-up consisted of physical examination and laboratory tests every 3 months, and chest and abdominopelvic CT every 6 months. All study patients were followed for at least 2 years by a gastroenterologist at our hospital or an affiliated hospital.

Data analysis

We referred to CT as the gold standard for gastric cancer recurrence, and reviewed medical records of each patient to collect demographic and clinical information including age, sex, tumor site (fundus, body, antrum or diffuse), presence of signet-ring cells, pathological stage (pT and pN), presence of elevated tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19–9), and endoscopic findings. We reviewed findings of chest and abdominopelvic CT for each patient from the first to the last scan. Abdominopelvic CT generally covers the dome of the diaphragm and inferiorly.

CT protocol and imaging evaluation

Contrast-enhanced CT using an intravenous non-ionic iodine-containing contrast agent was performed in addition to plain CT unless contraindicated. All axial CT images were acquired from 0.5-mm collimation reconstituted with a slice thickness of 2 mm. Images were interpreted by two radiologists (H.M. and G.N.; 7 and 19 years of experience as a radiologist, respectively) who were unaware of CEA and CA19–9 levels, in order to assess subtle recurrence. A consensus reading was performed when the findings were equivocal.

The sites of recurrence (local, liver, peritoneum, abdominal or thoracic lymph node, abdominal or thoracic bone, lung, pleura, and other site) were recorded, and the metastatic pattern was recorded when sites multiplied over time. A total of 2365 CT scans with a scan range from chest to pelvis were obtained for all patients. The average number of CT scans was 6.58 per patient (range, 1–28 scans), and 280 patients (78 %) had more than 4 scans.

Our criteria for CT features of recurrence or metastasis were as follows:

1. Recurrence was defined as a lesion that grows over time irrespective of adjuvant chemotherapy or a lesion that decreases in volume after chemotherapy, and metastasis to an organ as the presence of such a lesion in that organ.
2. Peritoneal metastasis was defined as the presence of omental fat stranding or clustered tiny nodules with or without ascites.
3. Lymph node metastasis was defined as lymphadenopathy with a short axis ≥ 1 cm in diameter that increased in size over time.
4. Pleural metastasis was defined as interlobular, septal or fissural thickening with multiple tiny nodules.
5. Bone metastasis was defined as an osteolytic, osteo-

plastic or mixed bone lesion that grew over time.

6. Pulmonary metastases were defined as round or lobular pulmonary nodules that grew over time.
7. Local recurrence was defined as the presence of a tumor at an operative site such as an anastomotic site.

Time to recurrence

Time to recurrence was defined as the period from the date of surgery to the date the first recurrence was detected on chest and abdominopelvic CT. Patients with recurrence were divided into three subgroups by pT (pT1 + pT2, T3, and T4), and similarly into three subgroups by pN (pN0 + N1, N2, and N3) to compare time to recurrence in those subgroups.

Tumor markers

Tumor markers (CEA and CA19–9) were measured at each visit, within 2 weeks after follow-up CT. Recurrence was suspected when either or both of those markers met criteria for elevation. Tumor marker elevation was defined as three consecutive increases or an increase exceeding the threshold (CEA: 5.0 IU/ml, CA19–9: 35 IU/ml). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CEA and CA19–9 for recurrence were calculated.

Esophagogastroduodenoscopy (EGD)

EGD was performed by a gastroenterologist at our hospital or an affiliated hospital. Additional biopsies were performed as needed and recurrence was diagnosed pathologically.

We evaluated the following outcome measures: (1) clinicopathological characteristics of patients and number of patients with recurrence for each characteristic, (2) postoperative variables predictive of thoracic metastases in patients with recurrence, (3) mean times to recurrence for pT- and pN-based subgroups, and (4) whether tumor markers and esophagogastroduodenoscopy (EGD) findings can be sufficiently reliable indicators of recurrence.

Statistical analysis

Statistical analyses were performed with JMP® Pro 15.1.0 software (SAS Institute Inc., Cary, NC, USA). The chi-square test was used to evaluate whether each clinicopathological characteristic was associated with postoperative recurrence and whether each clinicopathological and each abdominal metastatic site was a factor significantly correlated with thoracic metastases. The Kruskal-Wallis test was used to compare time to recurrence. All p values less than 0.05 were considered as statistically significant.

RESULTS

The average age at diagnosis was 70.2 years (range, 32–93 years), and most patients were male (67 %). Tumors were located at the gastric fundus in 22 (6 %) patients, gastric body in 233 (65 %), gastric antrum in 101 (28 %), and diffusely in the remaining 5 (1 %). Pathologically, 127 patients had signet-ring cells, and the remaining 234 patients did not. The stage was T1 in 214 patients, T2 in 46, T3 in 66, and T4 in 35. The nodal status was N0 in 241 patients, N1 in 37, N2 in 44, and N3 in 39. Radiologic and clinical follow-up periods ranged from 7 to 84 months, with a median period of 41 months, and the average CT follow-up interval was 7.4 ± 5.5 months.

Of the 361 study patients, 42 (12 %) experienced recurrence. The recurrence rate differed very little between male and female patients (n = 27, 11 % vs n = 15, 13 %; p = 0.66) and between patients with and without signet-ring cells (n = 15, 12 % vs n = 27, 12 %; p = 0.94). The tumor site associated with the highest recurrence rate was the diffuse type (fundus: n = 3, 14 %; body: n = 23 10 %; antrum: n = 12, 12 %; diffuse: n = 4, 80 %; p = 0.004). Higher T stage and/or N status was associated with a higher recurrence rate (pT1: n = 3, 1 %; pT2: n = 3, 7 %; pT3: n = 22, 33 %; pT4: n = 14, 40 %; p < 0.0001) (pN1: n = 4, 2 %; pN2: n = 4, 11 %; pN3: n = 14, 32 %; pN4: n = 20, 51 %; p < 0.0001). Three factors were significantly associated with recurrence: tumor site, pT status, and pN status. The clinical and pathological characteristics of patients are summarized in **Table 1**.

Table 1 Clinicopathologic characteristics of patients and number of patients with recurrence for each characteristic.

Variable	Total number N	Number with recurrence N, (%)	*p*-value*
Median age (years)	71 (32-93)		
Gender			0.66
Male	243	27 (11 %)	
Female	118	15 (13 %)	
Tumor site			0.004
Fundus	22	3 (14 %)	
Body	233	23 (10 %)	
Antrum	101	12 (12 %)	
Diffuse	5	4 (80 %)	
Histological type			0.94
Signet ring cell	127	15 (12 %)	
Not signet ring cell	234	27 (12 %)	
UICC Classification (pT)			< 0.0001
pT1	214	3 (1 %)	
pT2	46	3 (7 %)	
pT3	66	22 (33 %)	
pT4	35	14 (40 %)	
UICC Classification (pN)			< 0.0001
pN0	241	4 (2 %)	
pN1	37	4 (11 %)	
pN2	44	14 (32 %)	
pN3	39	20 (51 %)	

* The chi-square test was used for statistical analyses.
UICC: Union for International Cancer Control

Among the 42 patients with recurrence, pN factor was more strongly associated with thoracic metastasis than pT factor in patients with N0–1 ($n = 278$) versus those with N2–3 ($n = 83$) ($p < 0.05$), and in those with T1–2 ($n = 260$) versus those with T3–4 ($n = 101$) ($p = 0.48$). Chest metastasis was not observed in any of the 278 patients with pN0–1, who accounted for 77 % of the overall study population, but was observed in 2 patients with T1–2. Sites of recurrence included pleural metastasis ($n = 5$), lung metastasis ($n = 5$), peritoneal dissemination ($n = 19$), bone metastasis ($n = 3$; abdominal $n = 2$, thoracic $n = 1$), liver metastasis ($n = 13$), lymph node metastasis ($n = 9$: abdominal $n = 8$, thoracic $n = 3$), and other metastases ($n = 5$). Six patients (14 %) had recurrence only in the chest region (1 patient with T1N3, 1 patient with T2N2, 2 patients with T3N2, and 2 patients with T3N3). One of three tumors in the fundus (33 %), 7 of 23 tumors in the body (30.4 %), 2 of 12 tumors in the antrum (16.7 %) and 3 of 4 diffuse tumors (75 %) involved thoracic metastases. Tumor site was not associated with thoracic metastases ($p = 0.19$). Results of univariate analyses of postoperative variables predictive of thoracic metastases in the 42 patients with recurrence are summarized in **Table 2**.

Among patients with pN2–3, pN and pT factors were no longer associated with thoracic metastases. Among abdominal metastatic sites including lymph nodes ($n = 7$), bone ($n = 1$), liver ($n = 9$), and peritoneum ($n = 16$), lymph node metastasis was associated with thoracic metastasis ($p = 0.0008$). Results of univariate analyses of pathological stage and recurrent sites predictive of thoracic metastases in 83 patients with pN2–3 are summarized in **Table 3**.

When thoracic metastases were divided into lung parenchymal metastases ($n = 5$), pleural metastases ($n = 5$) and thoracic lymph node metastases ($n = 2$), lung parenchymal metastases were associated with liver metastases ($p = 0.008$) and pleural and thoracic lymph node metastases were associated with abdominal lymph node metastases ($p = 0.004$ and 0.002 respectively). Results of analyses of abdominal metastatic sites associated with lung parenchymal, pleural, and thoracic lymph node metastases in 83 patients with pN2–3 are summarized in **Table 4**.

Mean time to recurrence was 12 months after resection. Among the 42 patients with recurrence, 38 patients (90 %) experienced recurrence within 2 years, and the remaining 4 patients (10 %) within 3 years. The mean times to recurrence for pT1+T2, pT3 and pT4 were 15.2 ± 8.8, 11.0 ± 6.7 and 11.9 ± 8.4 months and those for pN1+N2, pN3 and pN4 were 11.4

Table 2 Postoperative variables predictive of thoracic metastases in 42 patients with recurrence in univariate analysis.

Factor	Thoracic metastasis	*p*-value*
pN factor		0.043
N0-1 ($n = 8$)	0	
N2-3 ($n = 34$)	13	
pT factor		0.89
T1-2 ($n = 6$)	2	
T3-4 ($n = 36$)	11	
Tumor location		0.19
Fundus ($n = 3$)	1	
Body ($n = 23$)	7	
Antrum ($n = 12$)	2	
Diffuse ($n = 4$)	3	

* chi-square test

Table 3 Pathologic stage and recurrent sites predictive of thoracic metastases in 83 patients with pN2–3 in univariate analysis.

	Thoracic metastasis	*p*-value*
pN factor		0.58
N2 ($n = 44$)	6	
N3 ($n = 39$)	7	
pT factor		0.62
T1-2 ($n = 17$)	2	
T3-4 ($n = 66$)	11	
Abdominal metastatic site		
LN ($n = 7$)	5	0.0008
Bone ($n = 1$)	0	0.66
Liver ($n = 9$)	3	0.14
Peritoneum ($n = 16$)	2	0.7

* chi-square test
LN; lymph node

± 8.4, 12.1 ± 7.5 and 11.9 ± 7.2 months, respectively. There was no significant difference in times to recurrence between three subgroups for pT or pN ($p = 0.65$ and 0.90, respectively). Mean times to recurrence in subgroups are shown in **Table 5**.

A total of 448 EGD examinations were performed in 298 patients during follow-up. EGD indicated recurrence only in two of those patients. Those recurrences diagnosed by biopsy were not detected by follow-up CT. One recurrent lesion was anastomotic recurrence, but the other was a possible new gastric cancer. The sensitivity of tumor markers for detecting recurrence was 62.5 % (25/40), specificity was 92.1 % (268/291), PPV was 52.1 % (25/48), and NPV was 94.7 % (268/283).

Table 4 Abdominal metastatic sites associated with lung parenchymal, pleural, and thoracic lymph node metastases in 83 patients with pN2–3.

Abdominal metastatic site	Lung parenchymal	*p*-value*
LN (*n* = 7)	1	0.37
Bone (*n* = 1)	0	0.8
Liver (*n* = 9)	3	0.008
Peritoneum (*n* = 16)	1	0.96
Total	5	
	Pleural	
LN (*n* = 7)	3	0.004
Bone (*n* = 1)	0	0.8
Liver (*n* = 9)	1	0.45
Peritoneum (*n* = 16)	1	0.96
Total	5	
	Thoracic LN	
LN (*n* = 7)	2	0.002
Bone (*n* = 1)	0	0.84
Liver (*n* = 9)	0	0.54
Peritoneum (*n* = 16)	0	0.39
Total	2	

* chi-square test
LN; lymph node

DISCUSSION

In this study, recurrence after curative gastric resection was strongly dependent on tumor site, T stage, and N status. Diffuse type has been reported to be an independent risk factor for all types of recurrence, such as peritoneal, disseminated, hematogenous and locoregional recurrences [6]. However, the high recurrence rate in patients with the diffuse type in this study was actually associated with advanced stage, including two T3N3b, one T2N2, and one T4N2. Therefore, we assumed pathological stage rather than tumor site was a significant factor in recurrences. Although patients with gastric cardia cancer were likely to have lung metastases [7,8], those patients were excluded from this study because gastric cancer of the esophagogastric junction was not always clearly differentiated from Barrett adenocarcinoma, especially in advanced cases. This fact makes it difficult to conclude that pure gastric cancer of the esophagogastric junction is truly associated with thoracic metastases.

The pulmonary metastasis rate in this study was 1.4 % (5 of 361 patients), which is consistent with previously reported rates of 0.7 % (22 of 3076) [9], 1.0 % (193 of 20187) [5], and 2.1 % (17 of 808) [10]. Furthermore, our finding that pulmonary metastasis was associated with liver metastases was consistent with a report from Kong J.H [5] which showed a significant association between pulmonary metastasis and hepatic metastasis.

Table 5 Mean times to recurrence for subgroups by pT and pN.

	Number	Mean ± SD (Month)	*p*-value*
UICC Classification (pT)			0.65
pT1 + pT2	6	15.2 ± 8.8	
pT3	22	11.0 ± 6.7	
pT4	14	11.9 ± 8.4	
UICC Classification (pN)			0.90
pN0 + N1	8	11.4 ± 8.4	
pN2	14	12.1 ± 7.5	
pN3	20	11.9 ± 7.2	

UICC: Union for International Cancer
Control SD: standard deviation
* Kruskal-Wallis test

Retrospective comparison of patients with N0–1 ($n = 278$) versus those with N2–3 ($n = 83$) and those with T1–2 versus those with T3–4 showed that pN factor was more strongly associated with thoracic metastases than pT factor, and no patients with pN0–1 showed thoracic metastases. This result is main novelty of our study. The reason why abdominal lymph node recurrence was a significant factor for thoracic metastases in patients with pN2–3 was likely that both pleural and thoracic lymph node metastases were significantly associated with abdominal lymph node recurrence. According to a previous report, patients with pleural metastasis or lymphangitic metastasis had shorter survival with a 1.5–2-fold increased risk of death [5]. These results suggest that selective chest CT surveillance in patients at particular risk would significantly reduce radiation exposure and healthcare costs in follow-up of postoperative gastric cancer patients.

With regard to the diagnostic capability of tumor markers to detect gastric cancer recurrences, a prospective study by Takahashi Y [11] showed that CEA had 65.8 % sensitivity and CEA and/or CA19–9 had 85.0 % sensitivity. We similarly found that the sensitivity and specificity of tumor markers (CEA and/or CA19–9) for detecting recurrence were 62.5 % and 92.1 %, respectively. This indicates that tumor markers are not likely to be a suitable alternative to CT to detect recurrence, although monitoring postoperative patients based on tumor markers seems to be useful for prediction of recurrence.

Regarding EGD, only 1 of the 298 patients who underwent EGD had local recurrence detected by EGD alone. A previous study [12] showed that anastomotic recurrences were much less frequent than other recurrences (8 %). Therefore, EGD could play a limited role in postoperative gastric cancer follow-up.

In this study, 90 % of recurrences were detected within 2 years after resection, and even the remaining 10 % were detected by 3 years at the latest. These results suggest that cautious follow-up with CT is necessary for the first 2 years after gastric cancer surgery, which is in line with the recommendation in the NCCN guidelines. Our results are also consistent with reports by Jyewon Song [13] and Gian Luca Baiocchi [3] showing that most recurrence of postoperative gastric cancer occurs within 3 years. Although our study included fewer patients than these 2 studies, we can draw a stronger conclusion because in our study abdominopelvic CT was routinely performed for almost all patients and multiple primary cancer was excluded. However, a few studies have shown that gastric cancer recurred after 3 years; most notably, Ju-Hee Lee [14] observed late recurrence beyond 5 years after gastrectomy in 2.8 % of postoperative patients with gastric cancer. A possible explanation for their conflicting result, noted by the authors themselves, is that they may have missed dormant minimal residual disease in the first 5 years because they did not perform imaging examination for all patients routinely (physical examination, and laboratory tests including tumor markers, imaging, and endoscopy). Additionally, based on the lack of significant difference in time to recurrence at each pT stage and pN status in this study, all patients with postoperative gastric cancer required follow-up with CT regardless of their stage.

Our study has 2 limitations. First, most of the positive findings of recurrence and metastasis were based on our criteria, not on pathological examination. However, chemotherapy is often started when distant metastases are suspected by CT in clinical practice, in order to avoid performing a potentially unnecessary invasive biopsy for a suspected recurrent lesion. Second, our study was a single-center retrospective study in Japan. Our population had class imbalance, with a relatively larger number of patients in stage pT1 or pN0. This may be because population screening is performed widely in Japan and gastric cancer is detected at an earlier stage [15,16]. However, this imbalance likely had little effect on our finding that most patients with recurrence after curative gastric resection for gastric cancer experienced recurrence within 3 years regardless of their stage, as supported by previous reports in which all recurrences occurred in three years in 1058 patients after curative intent gastrectomy for T1–2N0 [12] and 88 % of recurrences occurred in three years in 488 patients who underwent R0 resection. However, larger multicenter studies are needed to conclude that chest CT could be eliminated from routine follow-up for patients with pN0–1.

In conclusion, abdominal lymph node recurrence as well as pN factor were significantly associated with thoracic metastases and actually none of patients with pN0–1 had chest metastases. These facts implied limited role of routine chest CT for those patients. Time to recurrence was not affected by pathological stage.

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Disclosure

Approval of the research protocol: deemed unnecessary by the Research Ethics Committee of Osaka Medical College.

We are willing to make our data, analytic methods, and study materials available to other researchers for the purposes of reproducing the results or replicating the procedure.

We did not preregister the research with an analysis plan in an independent, institutional registry. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of conflicts

The authors declare no conflict of interest.

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