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An Attitude Survey for the General Public and Medical Doctors Concerning Gathering a Family History and Genetic Counseling Service

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We are systematically collecting the family histories of cancer patients upon admission. Members of the familial tumor counseling service select patients with familial tumors to receive genetic counseling. An attitude survey was conducted among the general public and medical doctors concerning the collecting of family histories. As a result of analysis of the questionnaires set up in a web page for the general public some people felt an interrogative and disagreeable sensation when they were asked about their family history. Most people wanted to undergo genetic testing for cancer, or wanted to do it depending on the terms of testing. If a genetic test was positive, many people answered that they would inform their spouses, parents, and friends of the test results, but this tendency was weak for their parents-in-law or grandparents. The result of questionnaires administered to medical doctors showed that a small number of patients refused to complete the survey about the family history and a small number of doctors had felt a sense of guilt when surveying for the family history. This is a small pilot survey and does not necessarily represent the general population. A more discreet analysis is therefore required.

Key words : familial tumor, family history, questionnaire, web, genetic testing
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Original Article

Present situation of pTNM classification in Japan: Questionnaire survey of the pathologists of *Gan-shinryo-renkei-kyoten Byoin* (local core cancer hospitals) on pTNM classification

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pTNM classification is the most important element of surgical pathology. Internationally, the International Union against Cancer (UICC)-TNM is the standard TNM classification. In the present study questionnaires about the pTNM were sent to the pathology divisions of 288 institutions designated as *Gan-shinryo-renkei-kyoten Byoin* (local core cancer hospitals) on the basis of the *Cancer Control Act*. The questionnaire consisted mainly of questions about the TNM. There were 78 respondents, including 70 qualified pathology specialists, with a mean of 18.4 years of experience. The recognition rate of the important basic rules of the UICC-TNM were as follows: 'When in doubt, select the lower': 63.6% (49/77); 'Direct invasion to a lymph node is an N component': 61.0% (47/77); 'Only the extension of an invasive cancer is a T component': 45.5% (35/77). Few respondents knew the UICC criteria for judging whether multiple pulmonary lesions represent metastatic or multiple primary lesions. Only 26 (36.4%) of 77 pathologists were informed about cTNM routinely, suggesting that neither pathologists nor clinicians possess adequate knowledge about pTNM classification in many institutions. It is recommended that pathologists be informed about the rules and importance of pTNM through education, the revised Japanese classification of cancers, and self-assessment of their own institutes.

Key words: lung cancer, pTNM, stage, International Union against Cancer, uterine cervical cancer

The International Union against Cancer (UICC)-TNM classification (UICC-TNM) was developed by the UICC in cooperation with the American Joint Committee on Cancer (AJCC).[1–3] UICC-TNM is used internationally as the standard TNM classification. TNM and stage, a grouping of combined T, N and M according to vital risk, are essential for both research and intervention.[1,2] In Japan, cancer staging is reported on the basis of *Gan-toriatsukai-kiyakus* (Japanese classification of cancers: JC) for each tumor site in most institutes, which are also based on TNM system.

To be designated as *Gan-shinryo-renkei-kyoten Byoin* in Japan (local core cancer hospitals: LCCH), the *Cancer Control Act* requires LCCHs to perform hospital cancer registration. The registration is conducted using the UICC-TNM classification system.

In Japan little attention has been paid to the pTNM, although it is the most important component of surgical pathology. The handling of surgical specimens and the reporting of pathology findings are conducted in compliance with the JC at most institutes in Japan. JC is very useful for standardizing pathology reports, particularly for cancers of the stomach and large intestine.[4] Each JC is independent, however, and therefore the stage classification is conducted according to separate individual criteria. The absence of common rules may allow a pathologist to apply the criteria for the organ that they diagnose daily to other organs; for example, applying the criteria for a gastric cancer to a uterine cervical cancer. JC rarely have written criteria about points that are difficult to judge. JC have no help desk to respond to users' questions. In addition, JC cannot be used for international research or reporting because it consists of domestic rules. The UICC-TNM represents the international system. It has general rules and additional rules. The same rules are fundamentally used for all organs.[5] The UICC-TNM has a supplement book and a frequently asked questions (FAQ) section, and detailed rules are established according to various situations.[3] When stagers have further questions, the help desk can be contacted on the Web.[6] The same

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definitions used for the UICC-TNM have now been adopted for the TNM classification in various JC, for example thyroid cancer, the cancer of the head and neck, renal cancer, lung cancer, ovarian cancer and so on.

In the present study we administered a questionnaire survey (including quizzes) on pTNM classification to the pathologists of LCCH. The questions pertained to knowledge of the TNM classification itself and to the TNM staging of lung cancer. Although the survey was conducted only in Japan, it may be interesting for pathologists and other medical professionals abroad, because there have been no prior reports of questionnaire surveys of pathologists from cancer hospitals on the pTNM classification.

MATERIALS AND METHODS

Questionnaires on pTNM were sent to 288 LCCH in Japan that had been approved by 2007. The version that was translated into English and the summaries of the answers are shown in Tables 1–7. In the original Japanese version the inquiries did not have any number, but sequential numbers were then assigned for the purpose of the report. The major questions were about lung cancer because (i) the texts on TNM of the Japanese *Classification of Lung Cancer* by the Japan Lung Cancer Society (JCLC) are almost the same as those of the UICC-TNM;[7] (ii) the pTNM classification is complex;[1,2] (iii) lung cancer is an important cancer, because it is the leading and second leading cause of mortality in male and female subjects, respectively, in Japan;[10] and (iv) we assessed the pitfalls of the lung cancer pTNM classification in our previous study (N. Teramoto, R. Nishimura, H. Takahata, S. Sawada, T. Shinkai, unpubl. data, 2007).

RESULTS

We obtained 78 responses from 70 institutes by fax or mail. Each response was independent. The data from the authors' hospital (Shikoku Cancer Center) were not included. One response was not included in the total because it was a completely blank paper. In one response there were no answers to the questions pertaining to lung cancer because the response was from a pathologist of an institution that did not treat lung cancer patients. For 78 responses, the standard error at a risk rate of 0.05 is ±6.7% with a response rate of 10%/90%, ±8.9% with 20%/80%, and ±11.0% with 50%. For example, if 20% of 78 respondents selected answer A, it is estimated that 11.1–28.9% of the pathologists in Japan would select answer A at a risk rate of 0.05. Tables 1,2 list the questions and answers about the respondents themselves and institutions. Table 3 lists the questions and answers about the present situation of surgical pathology diagnoses at their institutions. Tables 4–7 outline the quizzes about and answers to the TNM classification. The correct answers to these quizzes are shown in bold underlined letters. The mean number of correct answers by correspondents to 19 of 20 questions was 9.4 ± 3.6 (1–17), excluding V-1, which was a subjective question.

Table 1 Section I: Inquiry about the respondents themselves

	Total
1. How many years have passed since you became a pathologist?	
Average: 18.4 years (0–40 years)	78
2. Are you a certified pathologist?	
Yes: 70 No: 8	78
3. What is your position at your institute?	
Full-time pathologist : 73, Part-time pathologist: 5	78
4. How do you rate your level of knowledge about lung cancer?	
Specialist: 2; Familiar: 4; average: 53; Little experience: 19	78
5. Do you think that you received enough education about TNM during your residency as a pathologist?	
Yes: 1 No: 70 No opinion: 7	78
6. Do you think you have attended a sufficient number of courses at academic conferences or workshops to learn about TNM?	
Yes: 1 No: 75 No opinion: 2	78

Table 2 Section II: About the respondents' institutions

	Total
1. How many beds are at your institute?	
average: 612 beds, (300–1200)	77
2. How many pathologists are working at your institute?	
average: 2.89 (1–16)	77
1 pathologist/institute: 16	
2 pathologists/institute: 21	
3. How many operated lung cancer specimens do you examine per year?	
Average: 63.4 (0–200)	75
4. How many operated uterine cervical cancer specimens do you examine per year?	
Average: 29.8 (0–130)	74

Respondents and institutions

There were 78 respondents with a mean length of experience of 18.4 years (Tables 1,2). Most of the 73 respondents were full-time specialists in pathology. Only one pathologist indicated that he had received satisfactory education about pTNM during his training to become a pathologist. Another indicated that he had received it at academic meetings.

Present status of surgical pathology diagnosis

Although pTNM is defined as a modification of cTNM on the basis of pathological findings, only 26 respondents (33.8%)

Table 3 Section III: Present status of pathological diagnosis of surgical specimens

		Total (*n*)
1. Do clinicians inform about cTNM on most cases?		
Yes: 26; No: 34; IDK: 17		77
2. Who classifies the T of pTNM of lung cancer?		
Pathologist: 55; Clinician: 20, Tumor registrar: 0; IDK: 2		77
3. Who classifies the M of pTNM of lung cancer?		
Pathologist: 9; Pathologist if possible: 29; Clinician in most cases: 29; Tumor registrar: 2; IDK: 7		77
4. Do you separately indicate the UICC-pTNM and JCLC-pTNM?		
UICC-TNM and JCLC separately	9	77
Only JCLC-TNM	38	
Only UICC-TNM	2	
Neither	17	
5. Who sections the surgical specimens?		
Pathologist: 67; Pathologist with surgeon: 4; Surgeon: 4; Laboratory technician: 2		76
6. Can you refer to the results of intraoperative lavage cytology while making a pathological diagnosis?		
Yes: 69 No: 7		76
7. Is the size of the lung cancer measured?		
Yes: 72 No: 5		77
7a. In the case of 'Yes', who determines the size?		
Pathologist: 62; Surgeon: 5; Pathologist with surgeon: 4; Laboratory technician: 1		72
7b. If the answer is 'No,' what is done instead?		
Transcription of the clinical size: 1; Size is not recorded in the report: 4		5
8. When is the tumor size measured?		
Size is measured on the gross examination of surgical specimens	43	77
Size is determined by mapping in the cut-out figure.	12	
Determination in HE specimens	9	
Not measured	5	
Others	7	
9. Do you routinely prepare tissue sections for screening of metastases to the peribronchial lymph nodes in the hilar region, in addition to preparing sections of the lymph node specimens collected separately?		
Yes: 49 No: 28		77
10. When pleural invasion is suspected, is the site of maximal invasion always excised?		
Yes: 76 No: 1		77
11. How is intrapulmonary metastasis from primary cancer of the lung differentiated from multiple primary lesions?		
Differentiated according to the UICC-AJCC criteria	8	76
Differentiated on an individual basis, but I know the UICC-AJCC criteria.	4	
Differentiated on an individual basis. I do not know the UICC-AJCC criteria.	42	
Not differentiated	15	
Others	7	

AJCC, American Joint Committee on Cancer; IDK, I do not know (includes no answer); JCLC, Japanese Classification of Lung Cancer; UICC, International Union against Cancer.

Table 4 Section IV: Quizzes concerning general knowledge of UICC-TNM

	% of correct answers	*n*	Ref
1. When in doubt between T1 and T2, T2 is chosen from the point view of benefit of the patient.			
Yes: 11, **No: 49**, IDK: 17	63.6	77	5
2. Direct invasion of cancer to the lymph nodes is regarded as an N component.			
Yes: 47, No: 17, IDK: 13	61.0	77	1,5
3. When cancer cell spillage into the body cavity occurs during the surgical procedure, the case is regarded as M1.			
Yes: 0, **No: 54**, IDK: 23	70.1	77	1,5
4. In patients in whom preoperative chemotherapy was efficient, pT is judged from the spread of the cicatricial tissue.			
Yes: 10, **No: 42**, IDK: 25	54.5	77	1,5
5. All primary malignant tumors (excluding hematopoietic neoplasms) of the tumor sites that have UICC-TNM classification can be classified according to TNM classification.			
Yes: 33, **No: 20**, IDK: 24	26.0	77	1,2,5

Bold underlined, correct answers. Ref: reference providing evidence for the correct answer.
IDK, I do not know; 'no response' was totalized as IDK; UICC, International Union against Cancer.

Table 5 Section Va: Quizzes concerning UICC-TNM of lung cancer

		% of correct answers	*n*	Ref
1. It is stated in the JCLC that TNM is the same as UICC-TNM for lung cancer.				
Yes: 14 No: 17 IDK: 46		—	77	[1,2,7]
2. It is stated in the AJCC staging manual that AJCC-TNM is the same as UICC-TNM for lung cancer.				
Yes: 13. No: 3, IDK:61		16.9	77	[7]
3. TNM in the Japanese Classification of Lung Cancer is the same as UICC-TNM.				
Yes: 27, **No: 17.** IDK: 33		22.1	77	[1,3,7]
4. Bronchioloalveolar carcinoma (BAC) is now defined as a non-invasive tumor according to the WHO tumor classification. Thus, how is pT of BAC classified?				
pTis	18	53.9	76	[6,8]
pT1	8			
The maximum diameter of the BAC is measured, and pT is decided from the size (diameter).	41			
Others	9			
5. The UICC-TNM supplement says that 'When size is the criterion for the cT/pT category, the size is the measurement of invasive component.' Then, how is pT decided in the case of infiltrating cancer with BAC (e.g. in the case of mixed BAC and papillary adenocarcinoma)?				
pT1	2	59.2	76	[6,8]
Only the size of the infiltrating cancer excluding BAC is measured to determine the T.	22			
The size including the BAC is measured to determine the pT.	45			
Others	7			
6. Pleural invasion is a T component. What are the criteria for T2 among the following?				
Extension to a site near the visceral pleura	1	43.7	77	[9]
Invasion of the elastic lamina of the visceral pleura.	31			
Exposure of tumor cells to the visceral pleural surface	37			
Invasion of the parietal pleura	2			
Others	6			
7. Microscopic examination of the lung cancer specimens revealed small cancer nodules at a site distant from the main tumor, which were not detected macroscopically. Both cancer nodules were pure papillary adenocarcinomas, composed of invasive cancer alone.				
Regarded as intrapulmonary metastasis	35	11.7	77	[1]
Not regarded as intrapulmonary metastasis	9			
Cannot say for certain without actual observation of the specimens under a microscope	29			
Others	4			

Bold underlined, correct answers. Ref: reference providing evidence for the correct answer.
IDK, I do not know. 'No response' was in totalized as IDK in 1–3 and omitted in 4–7.
AJCC, American Joint Committee on Cancer; IDK, I do not know (includes no answer); JCLC, Japanese Classification of Lung Cancer; UICC, International Union against Cancer; WHO, World Health Organization.

answered that they were informed about the cTNM by clinicians in most cases (Table 3). There were 20 respondents who indicated that they did not judge the pT by themselves (III-2). There were 71 respondents (93.4%) who indicated that they performed sectioning of surgical specimens by themselves (III-5). Fifteen respondents, however, indicated that the lung tumor size for determining T was not determined by pathologists, including five respondents who indicated that the size was not measured on pathological specimens (III-7). Twenty-eight respondents (36.4%) indicated that they do not prepare specimens of peribronchial lymph nodes from the hilar region, which are the first targets of lymph node metastasis of lung cancer (III-9).

Answer validation of the quizzes

Section IV: Quizzes concerning general knowledge of UICC-TNM

Section IV includes questions on general knowledge of the UICC-TNM (Table 4). When there is a doubt, the tumor must be classified into the lower category according to the UICC-TNM general rule No.4 (IV-1).[5] It is also an important rule of the UICC-TNM that direct invasion to lymph nodes is regarded as the N component (IV-2).[5] Neither of the two rules is specified in any of the JC. The correct answer rates were 63.6% and 61.0%, respectively, but considering that these questions had two choices, the number of pathologists who had sufficient knowledge for the rules will be much smaller. ypT is judged from the actual existing tumor, not from the cancer scar (IV-3).[1,5] Tumor spillage during surgery has no influence on the TNM of tumors except for ovarian tumors (IV-4).[1,5] Carcinoid, sarcoma and melanoma, as well as hematopoietic tumors, are excluded from the TNM classification in most tumor sites (IV-5) because they do not have a similar prognosis as the carcinomas of the same TNM.[1,2]

Section Va: Quizzes concerning UICC-TNM of lung cancer

Section Va includes questions about the TNM classification of lung cancer (Table 5). In the JCLC it is implied but not written clearly that the JCLC-TNM and UICC-TNM are the same.[7] We do not know the correct answer to V-1, but JCLC-

Table 6 Section Vb: Quizzes concerning intrapulmonary metastasis and size of lung cancer

	% of correct answers	*n*	Ref
Questions 8–12. Choose the case in general terms. A clue: Questions 8, 9 and 12 refer to the presence of cancer nodules in the same lobe, and questions 10 and 11 refer to the presence of cancer nodules in different lobes.			
8. Two tumor lesions not adjacent to each other were visualized at the time of preoperative CT. Examination of tissue specimens from both tumors revealed the same histological type of adenocarcinoma. The smaller node does not have BAC around it. If the smaller lesion is regarded as intrapulmonary metastasis, the case would be evaluated as pT4pN0cM0 and stage IIIB. If it is not regarded as intrapulmonary metastasis, the case would be evaluated as pT1pN0cM0 and stage IA. Which of the evaluations is valid?			
Regarded as intrapulmonary metastasis: 61			
Not regarded as intrapulmonary metastasis: 10	13.2	76	1,6
Others: 5			
9. Under the same conditions as those in Question 8, metastasis was detected in the #12 lymph node alone. If the smaller lesion is regarded as intrapulmonary metastasis, pT4pN1cM0 and stage IIIB. If it is not regarded as intrapulmonary metastasis, pT1pN1cM0 and stage IIA.			
Regarded as intrapulmonary metastasis: 59			
Not regarded as intrapulmonary metastasis: 8	78.7	75	1,6
Others: 8			
10. Under the same conditions as those in Question 8, metastases were detected in the #12 lymph node alone. If the smaller lesion is regarded as an intrapulmonary metastasis, pT1pN1pM1 (PUL) and stage IV. If it is not regarded as an intrapulmonary metastasis, pT1pN1cM0 and stage IIA.			
Regarded as intrapulmonary metastasis: 49			
Not regarded as intrapulmonary metastasis: 16	21.1	76	1,6
Others: 11			
11. Under the same conditions as those in Question 8, metastases were detected in #7 lymph node alone. If the smaller lesion is regarded as an intrapulmonary metastasis, pT1pN2pM1 (PUL) and stage IV. If it is not regarded as an intrapulmonary metastasis, pT1pN2cM0 and stage IIIA.			
Regarded as intrapulmonary metastasis: 54			
Not regarded as intrapulmonary metastasis: 11	71.1	76	1,6
Others: 11			
12. Under the same conditions as those in Question 8, metastasis was detected in the liver. If the smaller lesion is regarded as an intrapulmonary metastasis, pT4pN0cM1 (HEP) and stage IV. If it is not regarded as an intrapulmonary metastasis, pT1pN0cM1 and stage IV.			
Regarded as intrapulmonary metastasis: 61			
Not regarded as intrapulmonary metastasis: 8	80.3	76	1,6
Others: 7			
13. The size measured by CT was 3.2 cm, while the size after fixation at the time of resection was 2.8 cm. The lesion is evaluated as cT2, but pT is evaluated as pT1.			
Yes: 56, No: 11 IDK: 10	72.7	77	5
14. The size measured after fixation was 3.2 cm, while the size in the HE specimen was 2.8 cm.			
Yes: 12 **No:54** IDK: 11	70.1	77	5

Bold underlined, correct answers. Ref: reference providing evidence for the correct answer.
BAC, Bronchioloalveolar carcinoma; IDK, I do not know; 'no response' was totalized as IDK.

Table 7 Section VI: Quiz concerning extension of intra-epithelial component

	Answer
1 The extension of cervical cancer to the portio supravaginalis is a factor for classification as T2a in cases of cervical squamous cell carcinoma;	
a In the presence of histological evidence of carcinoma *in situ*, the lesion is evaluated as pT2a, if vaginal extension is suspected macroscopically.	5
b In the presence of histological evidence of carcinoma *in situ*, the lesion is evaluated as pT2a, even if vaginal extension is not suspected macroscopically.	32
c **When evidence of invasive squamous cell carcinoma of the vagina is present histologically, it is evaluated as pT2a, even if vaginal involvement is not suspected macroscopically.**	35
d When vaginal involvement is suspected macroscopically, the lesion is evaluated as pT2a, even if evidence of carcinoma in situ is absent histologically.	0
e When vaginal involvement is suspected macroscopically, the lesion is evaluated as pT2a, even if evidence of infiltration is absent histologically.	0
No answer	5

The correct answer is c. The percentage of correct answers was 45.5%. Four respondents marked letters a–c together. They were dealt with as 'b' because b includes all the conditions.

TNM is distinctly different from UICC-TNM on minor rules (V-3).[1-3] For example, see the answer for V-6 in the next paragraph. AJCC-TNM and UICC-TNM of lung cancer are identical (V-2). UICC and AJCC worked together to make the same TNM system for all organs in the sixth edition,[1] although there are small numbers of minor differences.

It is plausible to evaluate bronchioloalveolar carcinoma (BAC) as pTis, because it is now defined as a non-invasive carcinoma.[11,12] It is also plausible to measure the size from the invasive component alone according to the principles of UICC-TNM.[5] At the moment, however, BAC is exceptionally regarded as an invasive cancer in UICC-TNM (V-4, -5).[6,8] The T2 criterion of JCLC-TNM requires complete exposure of the tumor cells to the visceral pleural surface,[7] while that of UICC-TNM includes the invasion of the elastic lamina (V-6).[9] The frequency with which JCLC-T1 is UICC-T2 depends on the patients who undergo surgery at each institution. At Shikoku Cancer Center, for example, JCLC-T1 is UICC-T2 according to the criterion in approximately 5% of patients (N. Teramoto, R. Nishimura, H. Takahata, S. Sawada, T. Shinkai, unpubl. data, 2007). Microscopic nodules that cannot be confirmed macroscopically or radiologically, are not evaluated as intrapulmonary metastases (V-7).[1,5] The correct response rate was only 11.7%. The criteria of intrapulmonary metastasis are summarized in Table 8.

Section Vb: Quizzes concerning intrapulmonary metastasis and size of lung cancer

Questions V-8–12 include questions about the differentiation of intrapulmonary metastasis from multiple primaries (Table 6). These questions were offered with the sentences 'You may think that you cannot choose a correct answer without checking the actual specimens. But please select an answer that fits best to the rules in general terms'. The UICC-TNM FAQ section says 'A 2-cm primary adenocarcinoma with multiple deposits of adenocarcinoma in another lobe, negative lymph nodes and no other metastasis is M1' (Table 8).[9] But this is a cancer showing multiple deposits. According to the AJCC staging manual, a subject with 2 nodules can be regarded as having intrapulmonary metastasis if at least one of the following three criteria is met: (i) lymph node metastasis of the common lymphatic drainage; (ii) mediastinal metastasis; or (iii) extrathoracic metastasis (Table 8).[1] Therefore, case V-8 with N0M0 is not regarded as intrapulmonary metastasis (pT1N0M0).

Intrapulmonary metastasis within a lobe is T4, while that in different lobes is M1(PUL). Because case V-9 is T4N1M0 or T1N1M0, it is certain that two nodules were in the same lobe. Therefore, the metastasis to lymph node 12 (lobar nodes bronchi) is in a common lymphatic drainage. Case V-9 can be regarded as intralobular pulmonary metastasis (pT4N1M0) according to criterion A. In contrast, case V-10, pT1N1M1(PUL) or pT1N1M0 is a multiple primary case because the case involved two nodules in different lobes and lymph node 12 is not in common lymphatic drainage. None of the A-C criteria are met in case V-10 (pT1N1M0). Case V-11 with N2 (mediastinal metastasis) can be regarded as intrapulmonary metastasis even if the node is present in different lobes (criteria A and B; pT1N2M1). Case V-12 with distant metastasis is M1(PUL) due to criterion C (pTN0M1). The correct answer rates for V-8 and V-10 (right answer: 'Not regarded as intrapulmonary metastasis') were very low (Table 6). The right answer rates for V-9, -11, and -12 (correct answer: Regarded as intrapulmonary metastasis) were high, probably because 44 (57.9%) of the 76 respondents answered all the cases as intrapulmonary metastasis.

When pT is determined by tumor size, the size of unfixed material is used first, the size of a fixed tumor as next best if measurement of unfixed material is impossible, and the size on preparatory slides is used as a last resort (V-13, -14).[5,6] The size measured on CT is not used as the pathology size if the actual size of a pathology specimen can be measured.

Section VI: Quiz concerning extension of intra-epithelial component

This question was submitted as a quiz concerning uterine cervical cancer to conceal the fact that this question was actually about the extension of an intra-epithelial component. In general, the extension of an intra-epithelial component does not change the T (VI-1).[5,6] The correct answer to this question was given by 35 (45.5%) of the 77 respondents (Table 7).

Table 8 Criteria of intrapulmonary metastasis

Description	Ref
Microscopic nodules that are not found radiologically or macroscopically are not regarded as intrapulmonary metastasis.†	1,5
A primary adenocarcinoma with *multiple deposits* of adenocarcinoma in another lobe, with/without lymph nodal and/or distal metastasis is M1.‡	9
Two separate nodules are not likely to be metastatic without any of the following‡ A Lymph node metastasis of the common lymphatic drainage B Mediastinal metastasis C Extrathoracic metastasis.	1,6

†This rule is written in the AJCC staging handbook, Part IV. It is based on UICC-general rule No. 5.

‡Note that the rule for multiple deposits and that for two (or a few) nodules are different. The former will also be true for carcinomas other than adenocarcinoma. The latter is described only in the AJCC staging handbook but is also valid on UICC-TNM.[6]

AJCC, American Joint Committee on Cancer; IDK, I do not know (includes no answer); JCLC, Japanese Classification of Lung Cancer; UICC, International Union against Cancer.

DISCUSSION

Questionnaires were sent to the pathologists working in LCCH. When considering the mean number of beds (approx. 600) and the mean number of pathologists (approx. three; Table 2), and that these pathologists belonged to LCCH, the responders handle many cancer cases routinely. Because there were only 78 respondents, there was a standard error of approximately 10%, but the purpose of the questionnaire survey was not to precisely estimate the correct answer rate from the population. We consider the results of this questionnaire survey sufficient to represent Japanese pathologists' knowledge about pTNM. As shown by this questionnaire survey, there is insufficient knowledge about the UICC-TNM among pathologists in Japan, but we expected these results.

It is noteworthy that the percentage of correct answers to questions concerning the following important criteria was only approximately 60%, despite the fact that the question presented two choices: for example, 'When it is difficult to judge TNM, the lesion is classified into the lower category' (IV-1), 'direct invasion of the lymph node is an N component' (IV-2) and so on (Table 4). It was even less recognized that the extension of a non-invasive component of a carcinoma does not raise T (Table 7).

Because pTNM classification is assigned by modification of cTNM based on the pathological findings,[3] pTNM classification without information on the cTNM makes little sense. In >60% of the institutions, however, the pathology division was not informed on the cTNM by the clinical divisions, suggesting that not only pathologists, but also the majority of clinicians give little importance to evaluating the pTNM of the pathological specimens (Table 3). Judging whether multiple pulmonary lesions are multiple primary tumors or multiple metastases changes the stage of a lung cancer considerably. According to III-11, the differential diagnosis between intrapulmonary metastatic tumors versus multiple primary tumors is not based on the UICC-AJCC criteria or on any other common criteria, but rather on individual judgment in most institutes (Table 3). The results of judgment based on the UICC-AJCC criteria are not always the most appropriate in actual clinical cases. It is not justified, however, for each pathologist to decide pTNM on their own individual criteria, without knowing the common criteria. Because staging is based on the surveys of TNM and prognosis at many institutions, it is not possible to stage a case without using common criteria shared among institutions.[1,2] Accumulating information on cancers precisely staged on common criteria is essential to improving the reliability of the TNM system in the future.

When a pathologist explains the pathological findings of a cancer to a patient directly in the pathologist's office, pTNM assumes great importance, because it is the most important prognostic predictor. The prognosis is the major concern of patients. Appropriate sectioning of a surgical specimen is impossible without comprehension of the pTNM classification. Wrong pTNM will lead to deviations of cTNM. It goes without saying that pTNM classification must be determined by the pathologists who make the pathological diagnosis, not by clinicians or tumor registrars who do not actually examine the specimens.

The results of the questionnaire survey indicated the faults of the surgical pathology system in Japan. For the establishment of evidence-based medicine, pTNM must be standardized. TNM classification itself is not difficult (according to our experience from unpublished data). The certification test for a pathology specialist in Japan should include questions to test knowledge of TNM. Because most responders answered that they had not been educated about TNM at all, education through training sessions at conferences might also be useful. Most JC cite the texts of UICC-TNM of the organs, but the basic rules of UICC-TNM, which TNM stagers should know before use, are not described. The JC needs to include information explaining the importance of staging, a detailed explanation of the UICC-TNM, and a list of reference books.

In addition to questionnaire surveys, investigating the accuracy of actual recorded pTNM is necessary to determine whether the pTNM is being correctly used. The present survey was performed in Japan. It is not certain how much pathologists in other countries know about the rules of pTNM. It is recommended that the accuracy of pTNM be investigated to assure the quality assurance of pathological diagnoses.

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ORIGINAL CONTRIBUTION

Preoperative Radiation Response Evaluated by 18-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival in Locally Advanced Rectal Cancer

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PURPOSE: This study focuses on the prognostic survival value of postirradiation metabolic activity in primary rectal cancer as measured with 18-fluorodeoxyglucose positron emission tomography.

METHODS: From July 1995 to March 2002, all 59 patients underwent two series of fluorodeoxyglucose positron emission tomography: one before preoperative radiation (standardized uptake values-1), and the other two to three weeks after radiation (standardized uptake values-2). Standardized uptake values-1 and standardized uptake values-2 correspond to before and after radiation, respectively.

RESULTS: In univariate analysis, the following emerged as significant prognostic variables: with or without residual tumor, pathologic differentiation, with or without recurrence, standardized uptake values-2, and with or without lymph node metastases. In multivariate analysis, residual tumor and standardized uptake values-2 were significant prognostic factors for survival. The median survival and the five-year overall survival rate comparing standardized uptake values-2 values <5 *vs.* >5 were 95 *vs.* 42 months and 70 *vs.* 44 percent, respectively ($P=0.042$).

CONCLUSION: A significant survival benefit was observed in patients with low fluorodeoxyglucose uptake after preoperative radiotherapy in primary tumors of rectal cancer.

KEY WORDS: Positron emission tomography; Radiotherapy; Prognostic value; Standardized uptake values; Rectal cancer; Preoperative radiation.

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A number of studies have reported that preoperative radiotherapy (RT) reduces the recurrence rate for locally advanced rectal cancer.[1–6]

Several studies have suggested that in selected patients with low rectal tumors, high-dose preoperative RT might permit the resection of the primary tumor with a high rate of preservation of sphincter function.[7–11] Such treatment results could have survival rates similar to those observed with more radical surgery without increasing the risk of pelvic or perineal recurrences.

However, except for a single European trial, definitive improvement in overall survival has not generally been demonstrated with preoperative RT alone.[3,12]

The prognosis of rectal cancer is generally related to the degree of penetration of the tumor through the bowel wall and the presence or absence of nodal involvement.[13–16] However, diagnostic accuracy of tumor penetration and nodal status is not sufficient.[17]

Many other prognostic markers have been evaluated retrospectively in determining the prognosis of patients with rectal cancer, although most, including allelic loss of chromosome 18q or thymidylate synthase expression, have not been prospectively validated.[18–20]

In those cases of rectal cancer in which preoperative RT was administered, nodal involvement and penetration of the tumor seemed to be significant for prognosis as well.[21–25] Besides nodal involvement and penetration status, no definitive prognostic markers have been reported in the preoperative radiation setting for this malignancy.

Prognostic information available before surgery is useful to select the candidates for a more aggressive surgical approach, such as extended lymphadenectomy, as well as intensive postoperative adjuvant therapy.[26–30] Also, the identification before the start of the entire treatment course of subsets of patients who are at low or high risk for recurrence can help to optimize treatment. For high-risk subsets, a more aggressive preoperative approach,

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such as combined modality preoperative treatment should be considered. Few predictors have been reported for this use.

Several studies have now been reported claiming the potential of fluorodeoxyglucose–positron emission tomography (FDG-PET) in predicting treatment outcome after preoperative RT for malignant neoplasms, including rectal cancer.[31,32] However, no consensus has been established on the usefulness of FDG-PET in predicting survival outcomes.

This study was designed to clarify the role of FDG-PET as a prognostic tool for patients with rectal cancer treated with preoperative RT.

PATIENTS AND METHODS

Study Design

From July 1995 to March 2002, the authors prospectively enrolled 59 patients with primary rectal cancer deemed eligible for preoperative RT, on the basis of a clinically bulky or tethered tumor or on imaging-based evidence of T3–4 or N1 disease by use of transrectal ultrasound. The distance from the anal edge of the tumor to the anal verge was <3 cm in 11 cases, 3 to 5 cm in 42 cases, and >5 cm in 6 cases. All patients received 50 Gy to the pelvis and were subjected to two series of FDG-PET: one before preoperative RT, and the other two to three weeks after the treatment (days after radiotherapy ranged from 11–50; mean, 17; median 16). Surgery was performed 20 to 77 (mean, 43.3; median, 41) days after the completion of preoperative RT and 3 to 63 (mean, 26.2; median, 25) days after the second FDG-PET study.

The study was a prospective trial and had institutional review board approval. Informed consent was obtained from all patients.

Treatments

For RT, a 6-MV x-ray accelerator delivered 50 Gy in 25 fractions, 5 fractions per week during five weeks. Two AP/PA opposed fields were used as a Japanese conventional radiation technique for pelvic tumors. The clinical target volume included the entire pelvic cavity, anal canal, primary tumor, mesorectal and presacral lymph nodes, nodes along the internal iliac artery, lumbar nodes up to the level of the lower border of the fifth lumbar vertebra, and nodes at the obturator foramen. No chemotherapy was added to the RT in a preoperative setting. All surgeries were performed by colorectal specialists. Abdominoperineal resection with permanent colostomy was performed mainly for low rectal cancers located <5 cm from the anal verge, and for other rectal cancers mainly intersphincteric resection with coloanal anastomosis, according to surgeons' judgment. When residual tumor cells were found in the surgical resection margin, postoperative adjuvant 5-fluorouracil–based chemotherapy was performed.

Positron Emission Tomography, Standardized Uptake Values

All patients received two series of FDG-PET: one before preoperative RT, and the other two to three weeks after the treatment (days after RT ranged from 11–50; mean days after RT, 17±7.6).[33] 18-fluorodeoxyglucose (18F) was synthesized using the Cypris Model 370 Cyclotron® (Sumitomo Heavy Industries, Shinagawa-ku, Tokyo, Japan), and FDG with an automated FDG synthesizer based on the method reported by Harms and Starling[11] radiochemical purity was >95 percent. The physical characteristics of this machine have been described in detail in a previous study.[31] Patients fasted for at least 4–1/2 hours before PET scanning so that serum glucose levels were between 80 and 110 mg/ml. All studies were performed using a Headtome IV dedicated PET scanner® (Shimadzu Corporation, Kyoto-city, Kyoto, Japan) with seven imaging planes at 13-mm intervals, each 10-mm thick. The inplane resolution was 4.5-mm full width at half maximum (FWHM). The axial resolution was 9.5-mm FWHM and the sensitivities were 14 and 24 kcps/(micro Ci/ml), respectively, for direct and cross planes. Each transmission scan was performed for eight minutes. For injections, 333 to 444 MBq of FDG were introduced via the cubital vein. A series of static acquisitions for 6 minutes each were initiated 60 minutes after the injection, and the mean time for the main tumor lesion was fixed at a constant setting of 63 minutes.

PET Data Analysis

Cross-sectional sinogram data were corrected for dead time, decay, random coincidences, and attenuation. Image reconstruction was performed by using a filtered back-projection algorithm with a Hanning filter using a cutoff frequency of 0.3 and a 128×128 matrix. Several regions of interest (ROIs) were drawn manually on the hot spots of tumors. To minimize the partial volume effect associated with decreasing tumor sizes resulting from radiotherapy, the ROIs were set to have a number of pixels between 40 and 99. FDG accumulation was measured by using standardized uptake values (SUV) obtained by the following equation:

$$\text{SUV} = (\text{decay corrected PET value})/[(\text{injected dose})/(\text{body weight})].$$[33,34]

We defined SUVs in FDG-PET before preoperative RT as SUV_1 and two to three weeks after the treatment as SUV_2.

Pathologic Analysis

Analysis of the surgical specimen included a determination of the following parameters: 1) histologic type of the tumor; 2) degree of extension of the tumor through the rectal wall; 3) nodal involvement; and 4) status of proximal and distal margins. Pathologic response criteria were

Table 1. Univariate analysis

Factor	N	Relative risk	95% confidence interval	P value
Residual tumor				
+	8	1		
−	51	0.147	0.056–0.384	<0.0001
Differentiation				
Well	41	1		0.0011
Moderate	11	3.923	1.229–12.518	0.0210
Mucinous	4	6.14	1.57–24.012	0.0091
Poorly	2	23.093	4.09–130.371	0.0004
Unknown	1			
Recurrence				
+	31	1		
−	28	0.113	0.026–0.494	0.0038
Post-SUV	59	1.306	1.073–1.591	0.0079
SUV ratio				
>100%	4	1		
<100%	55	0.239	0.067–0.854	0.0276
LN				
+	30	1		
−	29	0.341	0.121–0.958	0.0411
Astler-Coller				
B1	10	0.21	0.027–1.63	0.1354
B2	18	0.315	0.088–1.132	0.0767
C1	4	1.123	0.247–5.097	0.8808
C2	26	1		0.1643
SUV ratio	59	1.014	0.994–1.033	0.1648
Pre-SUV	59	1.088	0.962–1.232	0.1788
Pathologic effect				
Grade 0	2	0.235	0.014–4.059	0.3193
Grade 1	44	0.102	0.012–0.868	0.0366
Grade 2	12	0.121	0.012–1.182	0.0693
Grade 3	1	1		0.1877
Sex				
Male	37	1		
Female	22	0.603	0.215–1.692	0.3363
Age (yr)	59	0.986	0.941–1.032	0.5392

SUV = standardized uptake values, LN = lymph node metastases.

defined as proposed by the Japanese Society for Esophageal Disease: Grade 0, no treatment effect; Grade 1, more than one-third viable tumor cells; Grade 2, less than one-third viable tumor cells; and Grade 3, no viable tumor cells.[35]

Statistical Analysis

Statistical analyses were performed by using StatView Dataset File version 5.0 J for Windows computers. Survival periods were calculated from the start of irradiation. The survival functions were estimated with the Kaplan-Meier method estimator, and log-rank tests were used to compare the survival distributions. Both univariate and multivariate analyses for survival were performed.

RESULTS

Pathologic effect and SUV ratio (SUV_2/SUV_1) were related statistically ($P=0.047$). Pathologic effect, however, showed no significant correlation with recurrence and survival. Histologic tumor type and SUV ratio were correlated and the ratio was >100 percent when the tumor type was poorly differentiated adenocarcinoma. Although recurrence rate tended to be higher with an elevated value of SUV_2, there was no significant association between them.

SUV ratio showed a tendency to be related with recurrence, and recurrence rate was of marginally higher significance when SUV ratio was >100 percent. Survival period was significantly short when SUV ratio was >100 percent ($P=0.0121$) and/or when SUV_2 was >5 ($P=0.0378$).

In univariate analysis, residual tumor, pathologic differentiation, recurrence, SUV_2 value, and lymph node metastasis were significant prognostic factors (Table 1). In multivariate analysis, no residual tumor and SUV_2 were significant prognostic factors for survival (Table 2). The survival curves comparing patients with *vs.* without residual tumor are shown in Fig. 1. Notably, when SUV_2 value was >5, overall survival was significantly poorer (Fig. 2). The median survival time and five-year overall survival rate comparing <5 *vs.* >5 SUV_2 value was 95.4 *vs.* 41.9 months and 70.4 *vs.* 43.6 percent, respectively ($P=0.042$).

DISCUSSION

SUV before RT and Prognosis

In this study, recurrence or poor prognosis was not related to high SUV before RT, which is in agreement with previously published reports. For head and neck cancers, Greven *et al.*[36] claimed that SUV before RT did not have any correlation with local control when examined for the entire group, primary site, or T stage (n=45). Others, however, have reported studies that differed from our results. Both Allal *et al.*[37] and Rege *et al.*[38] concluded that FDG uptake followed by RT, as measured by the SUV, had potential value in predicting local control and survival in head and neck carcinomas (n=63 and n=12, respectively).

SUV after RT and Prognosis

Recurrence or poor prognosis was related to high SUV after RT in our study. This result also concurs with earlier

Table 2. Multivariate analysis

Factor	Relative risk	95% confidence interval	P value
Residual tumor	0.302	0.094–0.973	0.0449
Differentiation			
Well			0.1552
Moderate	2.774	0.734–10.482	0.1326
Mucinous	2.875	0.574–14.406	0.1990
Poorly	10.486	0.988–111.283	0.0511
Recurrence	0.155	0.019–1.297	0.0854
Post-SUV	1.502	1.128–2	0.0054
SUV ratio <100%	0.675	0.107–4.268	0.6759
LN	0.362	0.080–1.637	0.1867

SUV = standardized uptake values; LN = lymph node metastases.

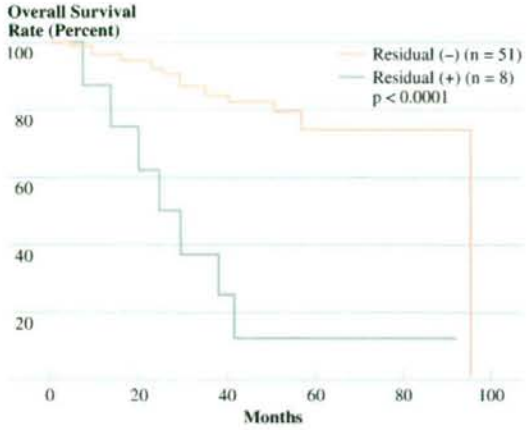


FIGURE 1. Overall survival curves comparing patients with *vs.* without residual tumor.

reports.[39,40] Higher SUV after preoperative RT predicts poor prognosis. Kunkel *et al.*[39] concluded that postirradiation FDG-uptake significantly predicted survival ($P=0.046$) and local tumor control ($P=0.0017$) in advanced oral squamous-cell carcinoma (n=35). Brun *et al.*[40] concluded that when a high initial tumor SUV was found, the reduction of SUV in the second PET examination might predict local tumor response in head and neck cancer (n=17). Swisher *et al.*[41] concluded that FDG-PET was predictive of survival in patients with esophageal carcinoma who had received preoperative chemoradiation ($P=0.01$; n=83). In our previous report,[32] only SUV_2 correlated with recurrence, although no significant correlation was observed in this study. It might be explained by the increased number of the patients involved to the study.

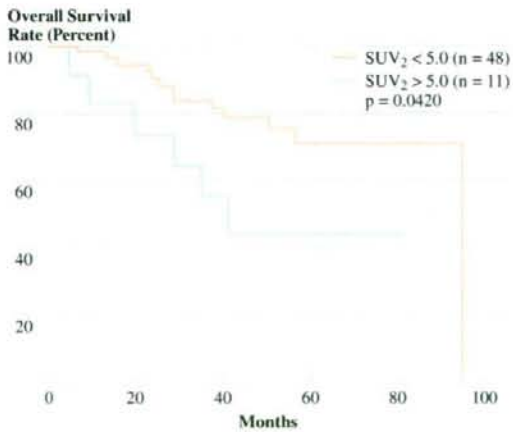
SUV before or after RT and Histologic Effects

SUV before or after RT was marginally correlated with histological effects. This finding is in agreement with previous reports. Kunkel *et al.*[42] reported a significant correlation ($P=0.045$) between post-RT FDG-uptake and histologic tumor regression was observed for mouth carcinoma (n=30). In their report, SUV>2.75 as a practical clinical threshold value for the identification of residual tumor resulted in a specificity of 88 percent, sensitivity of 68 percent, a positive predictive value of 94 percent, and a negative predictive value of 50 percent (in their report]).[41,42] In our actual follow-up data, a significant correlation could not be confirmed between post-RT SUV and patients' survivals. Brücher *et al.*[43] claimed an association for histology and survival in esophageal squamous-cell carcinoma (n=24). In responders, FDG uptake decreased by 72±11 percent; in nonresponders, it decreased by only 42±22 percent. Nonresponders to PET scanning (n=11) had a significantly poorer survival after resection than responders. Flamen *et al.*[44] also reported a correlation with histology and survival in locally advanced esophageal cancer (n=36). Response to chemoradiation as assessed by serial FDG-PET was strongly correlated with pathologic response ($P=0.002$) and survival ($P=0.087$).[44] In our study, SUV value after preoperative RT (SUV2) was significant in overall survival. In addition, the SUV ratio (SUV2/SUV1) showed an association with histopathologic effects and recurrence. These values are only available after the completion of preoperative radiation. In this respect, they may influence the surgical approach and postoperative adjuvant therapy. For example, if SUV1 was a prognostic marker, decisions could be made regarding preoperative treatment. SUV1 can control the entire treatment strategy, whereas SUV2 defines the surgical procedure and postoperative adjuvant therapy.

FDG-PET for Prediction of Survival in Rectal Cancer

The important implication of this study is that FDG-PET may be useful in assessing cytotoxic or ablative therapy. de Geus-Oei *et al.*[45] reported that a significant benefit ($P=0.017$) was observed in patients with low FDG uptake (SUV<4.26) with metastases of rectal cancer (of 152 patients, 67 were treated with resection of metastases and 85 with chemotherapy). A recent study from the Memorial Sloan-Kettering Cancer Center reported on monitoring the response to therapy with FDG-PET and the biologic basis of the change in FDG uptake of tumors in patients treated with neoadjuvant chemotherapy for hepatic colorectal metastases (13/42 evaluated patients underwent preoperative chemotherapy).[46] Fernandez *et al.*[47] concluded that post-resection screening by FDG-PET was associated with excellent five-year overall survival for patients undergoing resection of hepatic metastases from colorectal cancer (19 studies; 6,070 patients). Guillem *et al.*[48] from Memorial

FIGURE 2. Overall survival according to standardized uptake values-2 (SUV_2).



Sloan-Kettering Cancer Center suggested that FDG-PET might be useful in assessing the response of primary rectal cancer to chemoradiotherapy (n=15).

Denecke *et al.*[49] compared CT, MRI, and FDG-PET in the prediction of outcome of neoadjuvant radiochemotherapy in 23 patients with locally advanced primary T3/4 rectal cancer. The mean SUV reduction in responders (60±14 percent) was significantly higher than in nonresponders (37±31 percent; $P=0.03$). The sensitivity and specificity of FDG-PET in identifying response was 100 percent (CT 54 percent, MRI 71 percent) and 60 percent (CT 80 percent, MRT 67 percent). Positive and negative predictive values were 77 percent (CT 78 percent, MRI 83 percent) and 100 percent (CT 57 percent, MRI 50 percent) (PET $P=0.002$, CT $P=0.197$, MRI $P=0.5$). Additionally, Kalff *et al.*[50] evaluated the prognostic information obtained from the degree of change in tumor FDG-PET uptake induced by chemoradiation before radical curative surgery in 34 patients with T3/T4 rectal cancer. PET response was highly significantly associated with overall survival duration ($P<0.0001$) and time to progression ($P<0.0001$). Complete pathologic response was the only other statistically significant prognostic factor ($P<0.03$). The percentage of maximum SUV change after chemoradiation was not predictive of survival in partial metabolic response patients. Guillem *et al.*[31] tried to determine the prognostic significance of FDG-PET assessment of rectal cancer response to preoperative chemoradiation. The mean percentage decrease in SUV_{max} (ΔSUV_{max}) was 69 percent for patients free from recurrence and 37 percent for patients with recurrence ($P=0.004$). $\Delta SUV_{max} \geq 62.5$ was the best predictors of no-evidence-of-disease status and freedom from recurrence. Patients with $\Delta SUV_{max} \geq 62.5$ had significantly improved disease-specific and recurrence-free survival ($P=0.08$ and $P=0.03$, respectively).

The continued accumulation of clinical data on SUV for preoperative RT will contribute to establishing its usefulness. Studies in other malignancies, such as maxillary sinus carcinoma, are under consideration, for which preoperative RT is frequently performed.

CONCLUSION

A significant survival benefit was observed in patients with low FDG uptake (SUV<5) after preoperative radiotherapy in primary tumors of rectal cancer.

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MALT lymphoma

Radiotherapy for 41 patients with stages I and II MALT lymphoma: A retrospective study☆

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Abstract

Purpose: Mucosa-associated lymphoid tissue (MALT) lymphoma is a distinct disease with specific clinical and pathologic features that may affect diverse organs. We analyzed our recent experience with Stage I/II MALT lymphoma presenting in the stomach and other organs to assess the outcome following radiation therapy (RT) alone.

Patients and methods: Forty-one patients with Stages I (37) and II (4) disease were treated between 2000 and 2006. Patients with transformed MALT were excluded. The median age was 60 years (range, 25–86 years), male: female ratio 1:1. Presenting sites included stomach, 11; orbital adnexa, 21; thyroid, 1; other head and neck, 3; small bowel, 3; skin, 1; and rectum, 1. Thirty-five patients (85%) received RT-alone and 6 (15%) received antibiotics followed by RT. RT dose was 30 Gy in 20 fractions (fr) in all 41 patients. Mean follow-up time was 32.0 months (range, 2.1–162 months).

Results: A first complete response was achieved in all 41 patients. Only one patient died from bile duct carcinoma at 22 months from the start of irradiation for conjunctiva MALT lymphoma without recurrence of lymphoma. The other 40 patients were alive. Thirty-eight patients out of them were alive without recurrence. One patient with a duodenal lymphoma had a recurrence in non-irradiated distant sites at 1 month. Another patient with a bilateral eye lid lymphoma had a recurrence within radiation field at 41 months. The absolute local control rate with radiation was 98% (40/41 patients).

Conclusion: Localized MALT lymphomas have excellent prognosis following moderate-dose RT (30 Gy/20 fr).
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Keywords: Non-Hodgkin's lymphoma; MALT; Treatment; Radiation therapy

Mucosa-associated lymphoid tissue (MALT) type lymphoma is now incorporated into the Revised European–American Lymphoma (REAL) and the World Health Organization (WHO) classification systems [1,2] as extranodal marginal zone B-cell lymphoma, MALT type. It accounts for 4–13% of patients seen in individual cancer centers [3,4]. A recent nationwide study of malignant lymphoma among Japanese reported that it accounts for about 8% of all malignant lymphomas in Japan [5]. Although much knowledge has been gained in defining the clinical features, natural history, pathology, and molecular genetics of the disease in the last decade, the optimal treatment approach for MALT lymphomas is still evolving. The discovery of an association between *Helicobacter pylori* (*H. pylori*) infection and gastric MALT lymphoma, and tumor response with eradication of *H. pylori* [6–10], led to the novel concept that MALT lymphoma can be cured with removal of the underlying antigenic stimulus, the *H. pylori* infection. Predisposing conditions to MALT lymphoma are well recognized: Hashimoto's thyroiditis for thyroid MALT lymphoma [11] and Sjögren's syndrome for salivary gland MALT lymphoma [12].

Because 60–70% of patients with MALT lymphomas present with localized (Stage I or II) disease [3,13,14], and because there is a tendency for the disease to remain localized for a long time, local treatment, such as radiotherapy (RT), is often indicated. Previous retrospective studies demonstrated excellent local control rates and progression-free survival (PFS) after RT [15–30]. RT for orbital MALT lymphomas usually leads to late adverse events such as retinopathy, cataracts, or a dry eye [15–24]. Furthermore, there have been few published prospective trials evaluating the appropriate dose and field of RT for MALT lymphoma, except for patients with localized gastric disease [29]. Japan Radiation Oncology Group (JAROG) conducted a multicenter phase II study to evaluate moderate-dose (30.6–39.6 Gy) of RT between 2002 and 2004, depending upon the primary site and tumor bulk [31]. They concluded that moderate-dose RT was highly effective in achieving local control with acceptable morbidity in 37 patients with MALT lymphoma.

☆ Clinical investigation lymphoma

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Over the last decade and a half, works on multiple MALT lymphoma treated with RT series were published, and many of these words were specific to the organ that was treated. The radiosensitivity of MALT to radiation is also well established and the dose of 30 Gy to the stomach and even lower doses to orbital MALT lymphoma are standard of care. However, to date there are few well-documented reports of the efficacy of RT in this disease. We report the analysis of our experience of 30 Gy/20 fr involved-field RT for Stages I and II MALT lymphomas, emphasizing the excellent local control with radiation.

Methods and materials

This is a retrospective study. Forty-one consecutive patients with Stages I (37) and II (4) disease were treated between 2000 and 2006 in our institution. Patients with transformed MALT were excluded. Additionally, primary nodal marginal zone B-cell lymphoma, MALT type ($N = 2$) was also excluded. The median age was 60 years (range, 25–86 years) and male/female ratio was 1/1. Presenting sites included stomach, 11; orbital adnexa, 21; thyroid, 1; other head and neck, 3; small bowel, 3; skin, 1; and rectum, 1 (Table 1). Staging included site-specific imaging, enhanced CT or MRI in 39 patients (95%), gallium-68 scintigraphy in 7 (17%), F-18 2-deoxy-fluoro-D-glucose (FDG) positron emission tomography (PET) in 20 (49%), and bone marrow biopsy in 39 (95%). The diagnosis was made on the basis of hematoxylin and eosin-stained biopsy specimens supported by immunohistochemical analysis. Immunologic phenotyping on paraffin section was done for κ and λ light chain restriction and $CD20^+$, $CD5^-$, $CD10^-$, and cyclin $D1^-$, which in the context of the microscopic appearance, is consistent with MALT lymphoma.

Table 1
Patient and tumor characteristics

	No.	%
Anatomic location		
Stomach	11	27
Orbital adnexa	21	51
Thyroid	1	2
Other head and neck	3	7
Small bowel	3	7
Skin	1	2
Rectum	1	2
Maximum diameter of tumor		
≧5 cm	20	49
<5 cm	21	51
Sex		
Male	21	51
Female	20	49
Age		
≧60	21	51
<60	20	49
Stage		
IE	34	83
IEE	3	7
IIE	4	10
K-PS		
≧90%	39	95
<90%	2	5

Radiation method

The clinical target volume (CTV) was defined as an entire affected organ for lymohoma of the stomach or gross tumor volume (GTV) with at least 20 mm of margin for lymohoma of the small bowell, thyroid, other head and neck, skin, and rectum. Prophylactic irradiation for lymph node was not performed. The CTV was defined as the entire bulbar and palpebral conjunctiva for the orbital lymphoma with lesions confined to the conjunctiva or eyelids. The CTV was the entire orbital cavity for the retrobulbar lymphoma. A lens shield was placed unless the block compromised tumor coverage. One example of radiation dose distribution for gastric MALT lymphoma was shown in Fig. 1. RT dose was 30 Gy in 20 fr in all 41 patients regardless of the size of primary tumor. In the gastric lymphoma patients, the liver and kidneys were evaluated as the organs at risk. Of the 21 patients with orbital MALT lymphoma, 14 patients were treated with a cylindrical lens shielding (approximately 6–12 mm thick, depending on the electron beam energy). Lens shielding was placed 1 cm above the cornea.

Systemic therapy

Helicobacter pylori status was determined by the rapid urease test (Helico Check, Otsuka Co., Tokushima, Japan), serological testing (HM-CAP kit, Enteric Product, Inc., NY, USA) and ^{13}C-urea breath test before and after *H. pylori* eradication therapy. Thirty-five patients (85%) received RT alone and 6 patients (15%) that were positive of *H. pylori* infection in gastric lymphoma received antibiotics followed by RT. When patients were refractory to antibiotics or their cases were not associated with *H. pylori*, they were candidates for RT for gastric MALT lymphoma. Accordingly, cases in which *H. pylori* were completely eradicated only by antibiotic treatment were not indicated for RT. The determination of a failed response to *H. pylori* eradication therapy has so far been made at 12 months after the therapy, and RT has been applied to patients who did not achieve complete remission at that time. Patients who had simultaneous bilateral lesions were classified with Stage IEE disease according to other investigators' criteria [32–36].

Quality of follow-up

After the completion of radiotherapy, patients were followed at regular intervals. Careful clinical and ophthalmologic examinations were performed every 1–3 months for the first 2 years, every 4–6 months through year 5, and annually thereafter. For the patients with gastrointestinal MALY lymphoma, endoscopic, CT scanning and histological evaluation were performed immediately after radiotherapy and every 3–6 months thereafter. For the patients with orbital MALT lymphoma, orbital CT scanning or magnetic resonance imaging was recommended at 1 year after

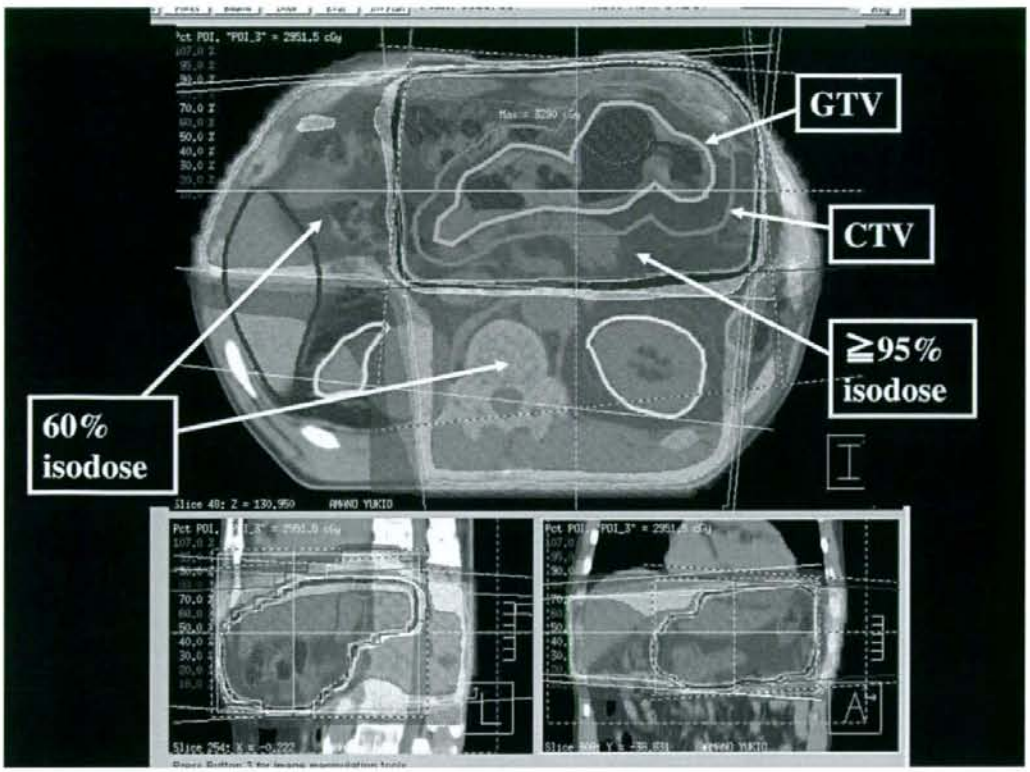

Fig. 1. Radiation dose distribution in the virtual simulation using a CT simulator of a gastric MALT lymphoma. The radiation portal consisted of a combination of the anterior–posterior direction and the lateral direction.

radiotherapy but was not required and other radiographic studies were performed as indicated clinically.

Statistical methods

The progression-free survival (PFS) was assessed using the method of Kaplan and Meier. Acute toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Late effects were graded according to the Radiation Therapy Oncology/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

Results

A first complete response was achieved in all 41 patients. Only one patient died from bile duct carcinoma at 22 months from the start of irradiation for conjunctiva MALT lymphoma without recurrence of lymphoma. The other 40 patients were alive. The 5-year overall survival rate was 96.7%. Thirty-eight patients out of them were alive without recurrence. The absolute local control rate with radiation was 98% (40/41 patients). Progression-free survival (PFS) curve of the 41 patients is shown in Fig. 2. The 5-year PFS rate for the entire group was 90.6%. Mean follow-up time was 3.3 years (range, 0.2–12.2 years).

The PFS took into account not only local relapses but also distant relapses. One relapse (the primary site: duodenum) was observed in non-irradiated distant sites at 1 month. The

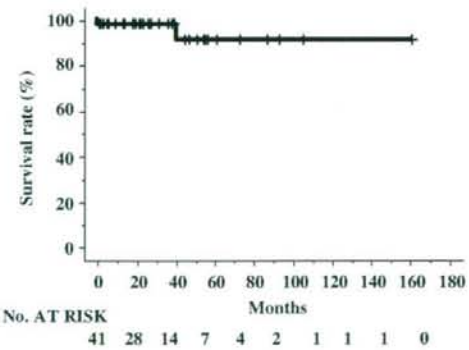

Fig. 2. Progression-free survival of the 41 patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue.

patient with a duodenal lymphoma had a recurrence in the abdominal para-aortic lymph node showing transformation into diffuse large B-cell lymphoma. After the recurrence, the patient was given systemic chemotherapy consisting of 6 cycles of R-CHOP regimen. It involved the monoclonal antibody rituximab, and the drugs: cyclophosphamide, doxorubicin, vincristine and prednisolone. After the salvage therapy, no recurrence has been detected until now for 71 months.

Another relapse (originated from bilateral eye lid) was within electron irradiation field at 41 months. The relapse lesion in the left lower eyelid was resected completely. The pathology remained unchanged. After the resection, no recurrence has been detected till now for 53 months (Table 2).

Acute toxicity and late complications

Radiation-induced side effects were negligible in the majority of the patients. No life-threatening toxicity (≧grade 4) occurred. Although acute radiation-induced conjunctivitis developed in 5 patients, none of them had severe later complications. The incidence of any later complications is listed in Tables 3 and 4. Cataract did not develop in any of the 14 patients who were treated with lens shielding. We observed three Grade 3 cataracts during this study period at 36, 46, and 162 months after the completion of RT.

Discussion

Because MALT lymphoma has been considered to be less responsive to standard chemotherapy than other aggressive lymphomas, RT has been used as the first line local treatment. Only for limited-stage gastric MALT lymphoma linking to *H. pylori* infection, *H. pylori* eradication therapy today has become recognized as a first-line treatment [50]. RT has been applied to patients who did not achieve complete remission after *H. pylori* eradication therapy.

This report on the RT treatment of MALT lymphoma in a variety of sites with involved-field RT of 30 Gy shows good clinical results. We have demonstrated that the PFS was 90.6% at 5 years. Our findings demonstrated that RT-alone was highly effective in achieving local control for localized MALT lymphoma. These favorable outcomes after RT are consistent with previous retrospective studies, which administered various doses of RT with a median of 25–40.5 Gy [15–24,26–30]. Many researchers concluded that 30 Gy of RT could achieve excellent local control.

Although several groups treating solely MALT lymphoma mentioned that 25–30 Gy is enough to control the disease [26,28], we also suggest that 30 Gy in 20 fr was appropriate for controlling MALT lymphoma without severe detrimental effects. Shu et al. [51] reported that the 10-year actuarial relapse-free survival, cause-specific survival, and overall survival rates were 93.1%, 97.9%, and 86.9%, respectively, for 48 orbital MALT lymphomas by RT of median 30.6 Gy (range; 5.4–30.6 Gy). Le et al. [52] reported 100% of the local control and recommended using a radiation dose of 30–30.6 Gy in 1.5–1.8 Gy fr for localized orbital MALT lymphoma. Zhou et al. [53] also reported 100% of the local control rate for orbital indolent lymphoma and concluded that a dose of 30 Gy was sufficient.

Table 2
Treatment and outcome characteristics

	No.	%
Radiation dose		
30 Gy/20 fr	41	100
Outcome		
Dead	1	2
Alive with recurrence	2	5
Alive without disease	38	93
The site of recurrence		
Within radiation field	1	2
Outside radiation field	1	2
Modality		
Electron	19	46
Photon	22	54
Energy		
6 MV	16	41
10 MV	6	15
6 MeV	18	44
12 MeV	1	2

Table 3
Acute and late toxicities in 21 orbital adnexa MALT lymphoma

	No. of patients (%)		
	Grade 0	Grades 1–2	Grade 3
Acute toxicities			
Dermatitis	18 (86%)	3 (14%)	0
Conjunctivitis/Corneitis	16 (76%)	5 (24%)	0
Total	13 (62%)	8 (38%)	0
Late toxicities			
Eyesight decline	19 (90%)	2 (10%)	0
Conjunctivitis/Corneitis	13 (62%)	8 (38%)	0
Cataract	16 (76%)	2 (10%)	3 (14%)
Total	7 (34%)	11 (52%)	3 (14%)

Table 4
Acute and late toxicities in 15 gastrointestinal MALT lymphoma

	No. of patients (%)		
	Grade 0	Grades 1–2	Grade 3
Acute toxicities			
Dermatitis	14 (93%)	1 (7%)	0
Mucotitis	8 (53%)	7 (47%)	0
Total	7 (47%)	8 (53%)	0
Late toxicities			
Edema	14 (93%)	1 (7%)	0
Intestinal obstruction	13 (87%)	2 (13%)	0
Pancreatitis	14 (93%)	1 (7%)	0
Ulcer	14 (93%)	1 (7%)	0
Total	11 (73%)	4 (27%)	0

Several phase II studies demonstrated antitumor activity of the purine analogs fludarabine and cladribine [37,38]. Chemotherapy alone (such as alkylating agent) series reported the significantly higher recurrence rate and cannot be the standard therapy for local advanced gastric MALT lymphoma [39–41]. Other groups have also shown that the anti-CD20 monoclonal antibody rituximab was effective for MALT lymphoma [42,43]. These findings also will be further elucidated in large-scale clinical trials.

According to Hellenic Cooperative Oncology Group's study [46], their patients received various commonly used chemotherapy regimens. Anthracycline-based treatments or rituximab did not offer any survival advantages. As rituximab therapy was started only recently, the follow-up, however, may have been too short to reveal any benefit. Other retrospective studies also observed no difference in efficacy between specific regimens [44,45], and several prospective phase II trials reported similar results [41,42,47,48].

The most frequent sites in this study were the stomach, the orbital adnexa, the head and neck, and the small bowel. Despite the low number of patients in our study, this observation is in agreement with other studies reporting the salivary glands, the orbit, the lung, the intestine and the skin as the most common nongastric lymphoma sites [13,43–46].

The next problem that should be resolved is the optimal target volume for MALT lymphoma. There are only a few studies that clearly demonstrate the target volume in the literature [16,21–23,25,27–29,31]. For gastric MALT lymphomas, the entire stomach and perigastric nodes are considered to be the target volume [28,29]. Olivier et al. [22] also delivered RT to the affected parotid gland with or without the first-echelon node for parotid lymphoma. On the one hand, Pfeffer et al. [49] showed that 4 of 12 patients with orbital lymphoma who received partial orbital irradiation experienced recurrence. Thus it seems reasonable that the target volume for MALT lymphoma should include the entire affected organ.

Conclusion

In conclusion, the results from this retrospective study confirm that RT was highly effective in achieving local control for localized MALT lymphoma, and 30 Gy in 20 fr was appropriate for controlling MALT lymphoma without severe detrimental effects.

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