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Should All the N3 Lymph Nodes Group Metastasis Be Regarded as Distant Metastasis (M1) in Curatively Resected Gastric Cancer?

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Recently, metastasis to N3 lymph nodes group was regarded as distant metastasis by the new TNM staging system due to poor overall survival. However, the 5-year overall survival rate of patients with metastasis to N3 groups was 34.5% after curative surgery. Moreover, in patients with metastasis to lymh node subgroups of #12, #13, #14, the overall 5-year survival rate increased upto 47.2% after curative resection and adjuvant chemotherapy. This was similar to that of the patients with metastasis to N1 and N2 lymph nodes groups. But in these highly tumor burden states, no survival benefit was found with the addition of immunotherapy to chemotherapy as we achieved in stage II and III. Therefore, we suggest that, at least, metastasis to #12, #13, #14 lymph nodes subgroups should not be categorized as a distant metastasis. And in these situations, active curative radical surgery with extended lymphadenectomy and adjuvant chemotherapy are recommended.

Key Words: N3, distant metastasis, extended lymphadenectomy

The overall 5-year suvival rate of the stomach cancer patients has not changed significantly over the last three decades and remains at 10~15% worldwide (Hirayam *et al.* 1980). Meanwhile, over the past two decades, the Japanese Research Society for Gastric Cancer (JRSGC) has improved overall 5-year survivals up to 50% following surgery (Miwa, 1979; Kajitani and Miwa, 1979; Takayoshi *et al.* 1983). One possible explanation for this difference is a high detection rate of early gastric cancer due to the active mass survey system (Kodama *et al.* 1981; Abe *et al.* 1984). But, none the less, stage for stage, Japanese patients survive longer than Western patients (Craven and Cuschieri, 1984); therfore second explanation might be the radical surgery used in Japan, which includes extensive systematic lymphadenectomy (Kodama *et al.* 1981). This accurate grouping of the lymph nodes with the standardization of surgical treatment has made a big difference in compared to the survival rate of Western countries.

In Korea, where stomach cancer is the most common malignancy, the overall 5-year survival rate has consistently increased due to the implementation of radical curative resection as proposed by the JRSGC (1981) and adjuvant treatments such as chemotherapy and immunotherapy. Recently, we reported an improved overall 5-year survival rate in stage II-III gastric patients after curative surgery with adjuvant chemoimmunotherapy (Kim *et al.* 1991). But the overall result of stomach cancer treatment is still far from satisfactory in Korea. The

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most important cause of this poor survival is that the majority of patients are at an advanced stage of the disease whether they can be resected (T4b/N2-3) or not (M1). According to Jananese results, patients with metastasis to N3 lymph nodes group by TNM staging (Beahrs and Myers, 1983) showed poor prognosis when they could not been managed by curative resection (Miwa, 1979; Nakajima and Kajitani, 1980; Miwa, 1984; Maruyama *et al.* 1987; Noguchi *et al.* 1989). However, if curative resection (R3/R4) could be performed, especially in patients with metastasis to #12, #13, #14 subgroups, the 5-year survival rate increased to 35~40% (Maruta and Shida, 1967; Okajima, 1977; Jinnai, 1980) which is a very hopeful result for our most advanced patients. But recently N3 group category has been regarded as distant metastasis (M1) by the new TNM classification (Beahrs and Myers, 1987). This change causes two other points to be changed also; one is that now there is a no rationale for the R3/R4 resection in a curative intent, although it could be a 'relative curative resection'. And the other is that the definition of adjuvant chemotherapy performed in patients with metastasis to N3 lymph nodes group should be changed to the palliative treatment. These new definitions can be as inadequate rationale in patients who might have some chance for the cure of diseases with an extensive trial as we and the Japanese groups have done.

Therefore, to evaluate the validity of this change of staging system in Korea, we analyzed the survival of our patients with metastasis to N3 lymph nodes group in the following aspects; 1) comparison of the survival of patients with palliative resection and curative resection, 2) analysis of the survival according to the extent of lymph node metastasis and 3) evaluation of the role of adjuvant chemoimmunotherapy.

PATIENTS AND METHODS

From September 1, 1983 to August 31, 1990, 63 patients were staged as metastasis to N3 lymph nodes group. The specimen was subjected to detailed pathologic examination which identified depth of invasion, nodal status, marginal involvement and histologic type of the tumors. Lymph node involvement was categorized as N1-N3 according to the AJCC (Beahrs and Myears, 1987) definitions (hepatoduodenal, retropancreatic, mesenteric, para-aortic lymph nodes) and again as #12-#16 accoding to the Japanese "General Rules" (n3; #12 hepatoduodenal, #13 retropancreatic, #14 lymph nodes around the mesenteric root, n4; #15 lymph nodes around mid-colic artery, #16 para-aortic lymph nodes) (JRSGC 1981) (Table 1). The tumor stage was determined finally by the pathologic TNM system. The operation was categorized as either a potentially curative resection or as a palliative resection by surgeons and pathologists as defined by the JRSGC. Curative gastrectomy includes ① no involvement of surgical stumps, ② sufficient lymphatic dissection (R-number≥N-number) ③ no distant metastasis ④ removal of involved adjacent organs and structures by combined enbloc resection ⑤ no gross residual disease. Tumor type and differentiation was evaluated by the WHO criteria (Oota and Sobin, 1977). After curative resection, chemotherapy was administered with FAM regimen (5-fluorouracil 1000 mg/m² 24 hr infusion for day 1-3, Adriamycin 40 mg/m² IV bolus day 1 g 3 weeks, Mitomycin 8 mg/m² IV bolus day 1 g 6 weeks) for 2 years. Poly-AU was combinated as immunotherapy (Fig. 1). Patients were randomized by T-factor for

Table 1. Numbering of upper abdominal lymph node stations

TNM N3	Station number by JRSGC	
Hepatoduodenal lymph nodes	#12	n3
Retropancreatic lymph nodes	#13	
Lymph nodes around the mesenteric root	#14	
	#15 (lymph nodes around mid-colic artery)	n4
Para-aortic lymph nodes	#16	

Arm A : Chemotherapy
5-fluorouracil 1000 mg/m² 24 hr IV infusion q 3 weeks for 24 months
Adriamycin 40 mg/m² IV q 3 wks×12 cycles
Mitomycin 8 mg/m² IV q 6 wks×12 cycles
Arm B : Chemoimmunotherapy
Chemotherapy ; same as arm A
Immunotherapy ; poly AU 100 mg IV q wk ×6 cycles, starting on day 4 after first chemotherapy, and 50 mg IV q wk ×6 cycles, 6 months later

Fig. 1. Adjuvant treatment regimen after curative resection.

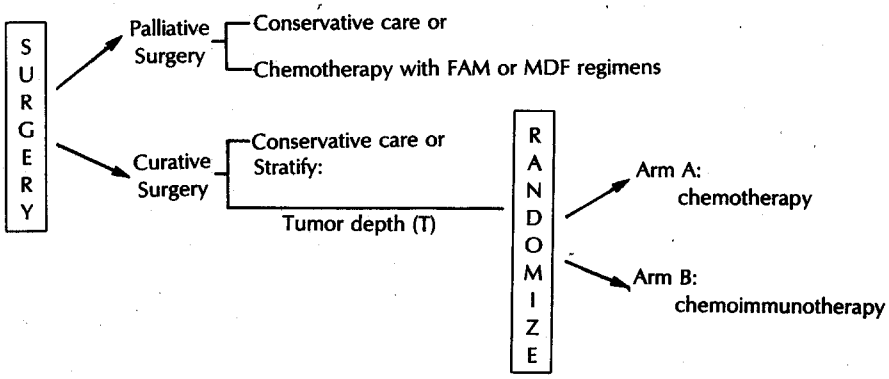

Fig. 2. *Treatment scheme of the patients.*

the immunotherapy. In palliatively resected patients, chemotherapy was performed with FAM regimen (5-fluorouracil 1000 mg/m² 24 hr infusion for day 1-3, Adriamycin 40 mg/m² IV bolus day 1, Mitomycin 8 mg/m² IV bolus day 1) or MDF regimen (5-fluorouracil 1000 mg/m² 24 hr infusion for day 1-3, cisplatinum 70 mg/m² day 1, Mitomycin 8 mg/m² day 2) in a non-randomized trial (Fig. 2). Statistical analysis was done using the independent two-sample t-test. The disease free duration was calculated from the day of operation to the documented day of disease recurrence of the last follow-up (May 31, 1991). Statistical analysis was performed by the product-limit estimation of survival from the Kaplan-Meier method and Log-rank test.

RESULTS

Patient characteristics

Of the 63 patients, 13 patients received a palliative resection with macro-(R) or microresidual (r) diseases, and 50 patients received a curative resection. Among 13 palliatively resected patietns, macroresidual disease remained in 8 patients (fixed nodes 6; liver 1; fixed node and liver 1), microresidual disease remained in 3 patients (surgical stump 3) and both macro and microresidual disease remained in 2 patients (surgical stump and fixed nodes). Two patients were managed with conservative care without palliative chemotherapy, while 7 patients were managed with FAM regimen and 4 patients with MDF regimen. Among 50 patients with curative resection, 6 patients were managed with surgical management alone and the remaining 44 patients were randomized as to adjuvant treatment (23, chemotherapy; 21, chemoimmunotherapy).

The median age of the total patients was 56-years (range 23-74 years) and the male to female ratio was 1.9 : 1. The median tumor size was 5 cm in curatively resected patients and 7 cm in palliatively

Table 2. Patients characteristics

	Palliative resection	Curative resection			Total
		Observation	Chemotherapy	Chemo-immunotherapy	
Number of patients	13	6	23	21	63
Age(year)					23~69
median	58	62	54	55	56
range	41~67	49~74	29~67		23~74
Sex					
M : F	10 : 3	2 : 4	16 : 7	13 : 8	41 : 22 (1.9 : 1)
Tumor size(cm)					
median	7	5	5	5	5
range	5~12	4~6	1~13	1.5~12	1~13
Tumor location					
antrum, pylorus	8	3	15	12	38
body	1	3	4	3	11
cardia, fundus	1	0	1	2	4
diffuse	3	0	3	4	10
Tumor differentiation					
well	1	0	1	1	3
moderate	5	3	6	2	16
poor	3	2	11	14	30
signet ring	4	1	5	4	14
Tumor depth(T)					
T1	0	0	1	1	2
T2	0	0	5	3	8
T3	3	0	2	5	10
T4	10	6	15	12	43
T4a	9	5	14	11	39
T4b	1	1	1	1	4
Node involvement(N)					
#12	2	2	6	7	17
#13	3	4	8	8	23
#14	2	0	4	3	9
#15	0	0	0	3	3
#16	6	0	5	0	11

resected patients. There was a striking preponderance of distal location of the primary tumor; antrum and pylorus 38 (60.3%), body 11 (17.5%), cardia and fundus 4 (6.3%), diffuse type 10 (15.9%). In tumor differentiation analysis, the well-differentiated type was 3 (4.8%), the moderately-differentiated type was 16 (25.4%), the poorly-differentiated type was 30 (47.6%) and the signet ring cell type was 14 (22.2%).

In evaluating tumor depth (T), T1 was 2 (3.2%), T2 was 8 (12.7%), T3 was 10 (15.9%) and T4 was 43 (68.2%) (T4a 39, 61.9%; T4b 4, 6.3%). In evalu-

Table 3. Types of surgical treatment

	Curative (n=50)	Palliative (n=13)	Total (n=63)
Subtotal gastrectomy	35	6	41
subtotal gastrectomy+ omentectomy	34	6	40
subtotal gastrectomy+ omentectomy+splenectomy	1	0	1
Total gastrectomy	15	7	22
total gastrectomy+ omentectomy+splenectomy	11	6	17
total gastrectomy+ omentectomy+splenectomy+ distal pancreatectomy	4	1	5

Table 4. Lymph node resection of the patients

	Palliative resection	Curative resection	Total patients	P-value*
Total number of dissected lymph node	13	50	63	
median	45	43	44	
range	16~80	12~85	12~85	
mean±SD	45±21	43±15	43±16	0.69
Lymph node number with metastasis				
median	21	12	14	
range	8~55	1~51	1~55	
mean±SD	25±16	16±12	18±14	0.03
% of metastatic lymph node				
median	47	29	33	
range	31~100	3~88	3~100	
mean±SD	57±24	36±23	40±25	0.005
Follow-up duration(months)				
medain	10	22	20	
range	3~35	2~85	3~85	

* comparison between palliative resection group and curative resection group

ating maximum node metastasis area, #12 involvement was found in 17 patients (27.0%), #13 in 23 patients (36.5%), #14 in 9 patients (14.3%), #15 in 3 patients (4.8%) and #16 in 11 patients (17.5%) (Table 2). In curatively resected patients, subtotal gastrectomy was performed in 35 and total gastrectomy was performed in 15. In palliatively resected patients, subtotal gastrectomy was performed in 6 and total gastrectomy was performed in 7 (Table 3).

The total numbers of dissected lymph nodes

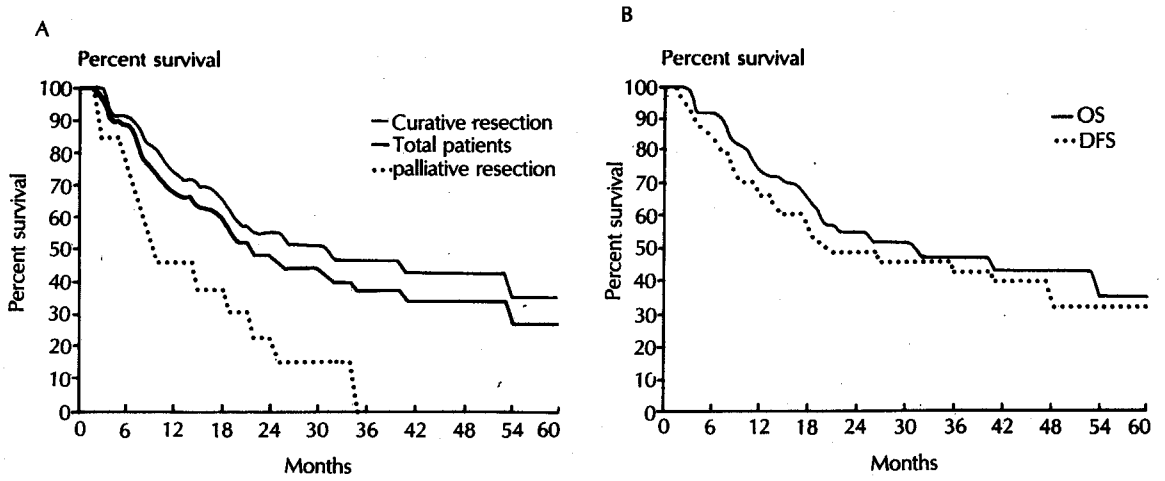

Fig. 3. *Survival of the patients according to treatment. A) Overall survival of all patients. B) Disease-free survival and overall survival of the patients with curative resection.*

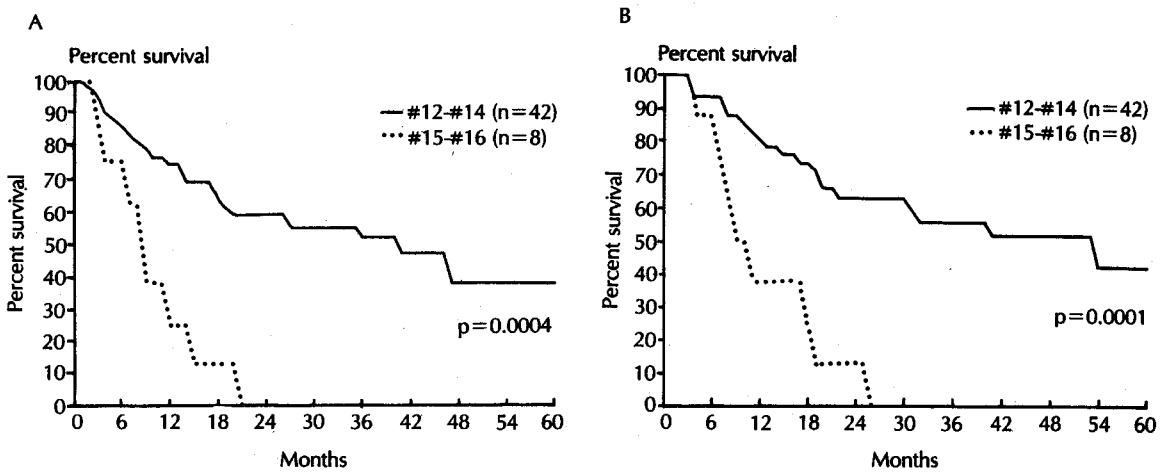

Fig. 4. Survival of the patients according to subgroup metastasis in patients with curative resection. A) Disease-free survival B) Overall survival.

were similar between the palliatively resected and the curatively resected groups. However, the number of metastatic lymph nodes and the percent fraction of the metastatic lymph nodes were higher in the palliatively resected group ($p = 0.03$, $p = 0.005$, respectiviely).

The median follow-up duration of the total patients was 20 months (3-85 months) (Table 4).

Overall survivals

The overall 2-year, 3-year, 5-year survival rate of the total patients are 46.3%, 37.2%, 27.5% respectively. The overall 2-year survival rate of the palliative resection patients was 15.4%, while no patient survived over 3 years. In curatively resected patients, the overall 5-year survival rate and the 5-year

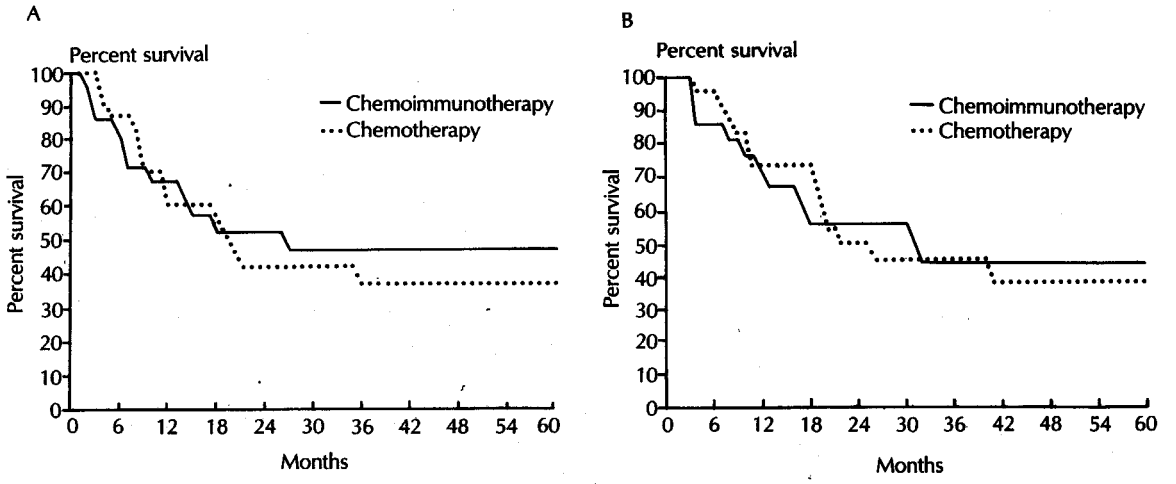

Fig. 5. *Comparison of the survival between chemotherapy and chemoimmunotherapy in patients with curative resection. A) Disease-free survival B) Overall survival.*

disease-free suvival rate were 34.5%, 31.6%, respectively, with a median survival duration of 31 months (Fig. 3).

Survivals according to the extent of LN metastasis in patients with curative resection

We compared the overall survival rates between patients with metastasis to #12-#14 (n3) and #15-#16 (n4) subgroups. The 5-year disease free survival rate of patients with metastasis to n3 subgroup was 47.2% while all the patients with metastasis to n4 subgroup recurred within 24 months ($p = 0.0004$). The overall 5-year survival of n3 was 41.2 % while all of the n4 patients died within 30 months ($p=0.0001$) (Fig. 4).

Comparison of adjuvant chemotherapy versus chemoimmunotherapy in patients with curative resection

Five-year disease free survivals were 36.5% and 46.8% in the chemotherapy group and in the chemoimmunotherapy group, respectively ($p=0.9445$). The overall 5-years survival rates were 38.2% and 44.4%, respectively ($p=0.7527$) (Fig. 5).

DISCUSSION

Since 1968, when Jinnai (1968) advised extended lymph node dissection, it has been believed to have contributed to increasing the survival rate of patients from advanced gastric cancer from the studies of the importance of lymphatic system in gastric cancer metastasis (Mine *et al.* 1970; Majima *et al.* 1972; Koga *et al.* 1983). Using this systematic lymph node dissection, the Japanese results for the overall 5-year survival of resected cancer patients was more than 90% in stage I, more than 50% in stage II and 30% in stage III. However, the results obtained from the Western countries during the same period has been disappointing due to lack of agreement about the importance of lymph node dissection (McNeer *et al.* 1974; Felding *et al* 1984; Douglass and Nava, 1985). This difference clearly shows the value of the absolute organ and lymph node specific radicality.

Regional lymph nodes of the stomach are classified into 3 groups by the TNM classification (Beahrs and Myers, 1983); N1 includes the perigastric lymph nodes and N2 means lymph nodes along side and at the roots of the main vessels to the stomach, namely, the left gastric, common hepatic, celiac and splenic arteries. N3 includes lymph nodes in the hepatoduodenal ligament, those behind the pancreas and those at the root of the superior mesenteric artery and para-aortic nodes. N3 groups is again subdivided into n3 (#12, hepatoduodenal; #13, retropancreatic; #14, lymph nodes around mesenteric root) and N4 (#15, lymph nodes around mid-

colic artery; #16, paraaortic lymph nodes)by JRSGC. Beginning the dissection of the N1 group, the 5-year suvival rate was 11%. Extending the dissection field to N2 group, it was 21% and to N3 group, it was 26.3%. But recently, N3 group was recategorized to M1-stage, namely M1 by the new TNM staging system (Beahrs and Myers, 1987).

This might be the results of the survival of patients with metastasis to N3 group similar to that of the patients with distant metastasis. The major factor for this poor prognosis is unresectability. Nakajima and Kajitani (1980) reported that only 2.0 % of their patients with N3 group metastasis could receive curative resection while 47.8% of patient received palliative resection. But the promising point is that, although the curative resection rate is low, if the curative resection could be done, the overall 5-year survival rate is 33-40% (Maruta and Shida, 1967; Jinnai, 1968; Okajima, 1977; Nakajima and Kajitani, 1980; Maruyama *et al.* 1989). These evidences show the significance of the complete clean-up the whole lymph nodes including N3, because positive nodal state does not preclude curative resection and long-term survival. In our series, the survival results showed similar trends. In palliatively resected patients, no patients survive longer than three years. But in curatively resected patients, the 5-year suvival rate was 34.6%, with a median survival duration of 31 months. Even if the median follow-up duration has so far been just 22 months, this result shows some promise.

The prognosis for patients with metastasis to n3 subgroup by Japanese criteria (#12, #13, #14) was good even though the belonged to the N3 group by TNM. This was fairly true if complete removal was performed (Okajima 1977, Maruyama *et al.* 1989). Because, in an attempt of curative resection, the degree of invasion of the gastric wall is an unalterable factor. But if metastasis to lymph nodes is confined to #12~#14 subgroups, this factor can be controlled by surgery. In our study, patients with n3 (#12~#14) subgroup metastasis gained more survival potential than n4 (#15 and #16) subgroup metastasis as measured by both disease-free and overall survival when curative surgery was performed. Our data suggests that, at least in patients with n3 (#12~#14) subgroup metastasis, extended radical resection should be aggresively attempted in order to achieve cure. But in patients with para-aortic lymph node, the situation is different. Only 6 (1.9 %) of 317 patients with para-aortic lymph node metastasis survived more than 5-year by means of extended lymph node dissection and chemotherapy (Miwa, 1984). This poor survival resulted from the difficulty of the complete removal of para-aortic lymph nodes. And recently, when the para-aortic lymph node metastasis is confirmed during operation, lymph node clean-up is not attempted based on the fact that the lymph node stream of the para-aortic lymph group is directed convergently towards cisternal chyli, forming a one unit. Therefore, today in our institution, para-aortic lymph node metastasis is considered to the non-curative even though it is removed with curative intent.

In contrast to us, the opinions of those in Western countries are still different as to the desirable extent of node dissection. The leading cause which precluded the extended radical surgery in Western countries was a high surgical mortality (Diggory and Cuschieri, 1985; Aretxabla *et al.* 1987; Dent *et al.* 1988). Fortunately, most Korean patients are thin with shallow abdominal cavities. Furthermore, predisposing severe heart, vascular, pulmonary, hepatic, renal and metabolic factors are not frequent. These factors allow extended radical surgery with few fatal post-operative complications. We did not experience any surgical mortality or severe complications in our 63 patients. These constitutional benefits are the same for Japanese, so their surgical mortality have been decreasing during the last two decades to about 1.0% today (Miwa, 1979; Maruyama *et al.* 1987; Soga *et al.* 1988; Mosika *et al.* 1989; Noguchi *et al.* 1989). Another possible reason to preclude radical surgery is a decrement of survival in line with the R (resection) number increment. But this is not a result from surgery but a tumor dissemination, because it has been found that the more gastric wall invasion, the more frequent regional lymph node metastasis was found regardless of the size or type of the tumors. Therefore, in spite of this R-number factor at least in Korea and Japan, a curative gastric resection with extensive lymphadenectomy can be safely performed with low surgical mortality.

In performing extended lymph node dissection, a special point to consider is the analysis of the relation between the degree of metastasis to lymph nodes to the degree of dissection of lymph nodes. If more nodes were dissected, there is a chance that more metastatic lymph nodes might be odd word choice and more patients with occult metastasis might be detected significantly. In our study, while the total number of dissected lymph nodes was not different between palliatively resected and curatively resected patients, the total number of cases of metastasis and the percent of metastatic

lymph nodes was higher in the palliative group, which had patients in more advanced stages of cancer. And the most common cause of palliative resection in our patients was node fixation which was impossible to resect completely. These data also support the fact that there is some relationship between the number of node-dissected and the number of nodes involved, thereby signifying the importance of systemic lymph node dissection.

In gastric cancer, a significant improvement in the five-year survival rate could be found in the lymph node positive group. And the best results with adjuvant chemoimmunotherapy were obtained in patients with stage II or stage III (Coombes *et al.* 1990; Kim *et al.* 1991). Therefore, we evaluated the additive role of immunotherapy with poly-AU in our patients with metastasis to N3 group. But we could not find further survival benefits from adding immunotherapy, although some trends of survival benefits were noticed in the chemoimmunotherapy group. A possible explanation is that the immunotherapy showed no role in highly tumor burden status such stage IV in our patients. We plan further study with more subjects to confirm this point.

In conclusion, our data suggest more survival benefits from curative radical surgery in patients with metastais to #12, #13, #14 (n3) subgroups than for patients with metastasis to #15 and #16 (n4) subgroups. So if n3 subgroup metastasis were categorized as distant metastasis and curative radical surgery was not performed, as in the Western countries, there might be a decreased chance of cure for these patients.

Therefore, we propose that metastasis to N3 lymph nodes group should be subdivided into two categories, namely as metastasis to n4 subgroup can be classified as M1 but in n3 subgroup, at least in Korea and Japan, where well-planned curative radical surgery and adjuvant chemotherapy can be performed with a low mortality rate. We could not find any survival benefits by adding immunotherapy to adjuvant chemotherapy in the highly tumor burden state (stage IV), unlike that which was found in stage II & III.

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