Yonsei Medical Journal
Vol. 31, No. 2, 1990

Comparison of Adjuvant Radiotherapy and Chemoradiotherapy Following Surgery in Stage IE and IIE Primary Gastrointestinal Tract Non-Hodgkin's Lymphoma

Hyun Cheol Chung[1], Jae Kyung Roh[1], Eun Hee Koh[1], Joo Hang Kim[1], Jee Sook Hahn[1], In Suh Park[1], Jin Sik Min[2], Kyung Sik Lee[2], Chang Ok Suh[2], John Jun Kyu Loh[3] and Byung Soo Kim[4]

Forty patients (median age 49.6 years) were treated for primary gastrointestinal lymphoma between 1979 and 1989. There were twenty-three cases of gastric lymphoma and seventeen cases of intestinal lymphoma. Following surgery, seventeen patients received postoperative chemoradiotherapy (ACOP) by the sandwich technique, seven patients received postoperative radiotherapy, and sixteen patients did not receive any other form of adjuvant treatment. Nineteen patients were stage IE and twenty-one were stage IIE. Stage IE disease was more prevalent in the gastric lymphoma group than the intestinal lymphoma group ($p<0.01$). At a median follow-up of 17 months (1-102+months), 17 of 19 stage IE patients and 15 of 21 stage IIE patients remained alive. The survival rate was 90% in the postoperative chemoradiotherapy group and 83.3% in the postoperative radiotherapy group at five years, and 42.7% in the surgery alone group at four years, which showed statistical significance ($p<0.01$, $p<0.05$, each). Statistically improved survival rates were achieved with a postoperative chemoradiotherapy modality in intestinal lymphoma ($p<0.01$), stage IIE ($p<0.01$), intermediate grade by NCI criteria ($p<0.01$), poorly differentiated lymphocytic lymphoma ($p<0.05$), and diffuse histiocytic lymphoma ($p<0.01$) according to Rappaport classification, compared to those of the surgically treated only group. Three local relapses occurred in the operation alone group, and one in the adjuvant radiotherapy group which occurred simultaneously with distant lymph node recurrence. The pathologic stage of all of these relapsed patients was stage IIE-2. These results suggest that adjuvant chemoradiotherapy in completely resected localized gastrointestinal non-Hodgkin's lymphoma can decrease local and systemic relapse resulting in long-term disease free survival and overal survival compared to operation alone.

Key Words: Gastrointestinal lymphoma, postoperative chemoradiotherapy, ACOP, sandwich technique

Although the gastrointestinal tract is the predominant site of extra-nodal non-Hodgkin's lymphoma, accounting for 30%-37% (Freeman *et al.* 1972; Aozasa *et al.* 1985), primary gastrointestinal lymphomas are relatively uncommon tumors. Primary gastrointestinal lymphoma cases are defined as all patients who present with gastrointestinal symptoms as a result of lymphomatous involvement, or who have an obviously predominant alimentary tract lesion (Dawson *et al.* 1961). Primary lymphomas arising in the stomach, small bowel, and colon represent only 1% to 4% of tumors in these anatomic locations (Loehr *et al.* 1969); however, they attract attention because of the potential for cure. Localized (stage IE & IIE) presentations are characterized by a low frequency of distant relapse. So with radical surgery alone, a 30%-60% cure rate has been noted (Loehr *et al.* 1969). Based on the high operative mortality and local recurrence rate, limited surgery and postoperative radiotherapy have been recommended since the 1960s (Herrman *et al.* 1980; Gospodarowicz *et al.* 1982). Furthermore, with the addition of postoperative chemotherapy to

Received January 8, 1990
Accepted March 7, 1990

Departments of Internal Medicine[1], General Surgery[2], Radiation Oncology[3] and Yonsei Cancer Center[4], Yonsei University College of Medicine, Seoul, Korea

Address reprint requests to Dr. H C Chung, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, 120-752

radiotherapy, the probability of cure has increased approximately 75%, and the local recurrence rate and operative mortality have been reduced (Shimm *et al.* 1983; Dragosics 1985; Aozasa *et al.* 1988). It therefore seemed logical to include chemotherapy in the treatment program for patients with localized gastrointestinal lymphomas. The choice of drugs in chemotherapy programs depends, to a degree, on the experience and studies of the group managing the patients.

This article compares the impact between the two combined multimodality treaments and the operation as a single modality on primary gastrointestinal lymphomas treated at our institution during the years 1979 to 1988.

PATIENTS AND METHODS

The clinical data of forty patients with gastrointestinal lymphoma who were admitted to Yonsei Medical Center and Yonsei Cancer Center between May 1979 and May 1989 and who had all the gross tumors resected completely with negative pathologic margins were reviewed. The initial evaluation of each patient included a complete history and physical examination, complete blood count with differentiated white blood cell and platelet counts, liver function test, chest roentgenogram, liver/spleen scan, abdominal ultrasound and/or computed tomography of the abdomen and bone marrow aspiration and biopsy. Of the forty patients, sixteen patients received operation only, seven patients received postoperative radiotherapy and seventeen patients received postoperative chemoradiotherapy.

The treatment program at our institution during the period of this study was to resect the primary lesion to decrease the possible risk of bleeding and perforation, and to permit a complete staging of the lymphoma if lymphoma was diagnosed preoperatively. Following recovery from surgery, postoperative adjuvant treatments were administered in twenty-four patients. In the postoperative chemoradiotherapy group, a sandwich technique was applied. Tables 1 and 2 summarize the treatment plan of the patients in this study.

The ACOP regimen was the principal chemotherapy protocol (Cabanillas *et al.* 1980; Nissen *et al.* 1983): cyclophosphamide 500mg/M² intravenously on day 1 and 8; adriamycin 40mg/M² intravenously on day 1; vincristince 1.4mg/M² intravenously on day 8; and prednisolone 60mg/M² orally on days 1 through 14. This cycle was repeated at 21 day intervals for a total of six to eight cycles.

Table 1. Chemotherapy protocol (ACOP)*

Adriamycin	40mg/M²	day 1
Cyclophosphamide	500mg/M²	day 1, 8
Vincristine	1.4mg/M²	day 8
Prednisolone	60mg/M²	day 1-14

* Cycles are repeated at 3 week intervals

Table 2. Scheme of the treatment schedule with sandwich technique

Week	1	4	7	10	13	16	19	22	
Chemotherapy cycle	1	2	3	radiotheraphy*		4	5	6	

* Irradiation of 3,500-4,000 cGy to the whole abdomen and 1,000 cGy to the primary focus

In gastic lymphoma, irradiation to the stomach-bed and the celiac trunk is the rule in stage IE, and the irradiation is extended to the whole abdomen in stage IIE. The total dose of 3000-4500 cGy is delivered in 4-6 weeks. In intestinal lymphoma, phase I consists of whole abdominal irradiation with a dose of 3,000 cGy. And phase II is a boosting dose to the primary site with a dose of 1000-1500 cGy in both stages IE and IIE. Radiotherapy was administered to twenty-four patients as the sole adjunctive therapy; radiotherapy alone was done in seven patients, and was combined with chemotherapy in seventeen patients after surgery.

Lymphomas were classified histologically according to the Rappaport criteria (Rappaport 1956) and grades were assigned in accordance with the Working Formulation (NCI 1982). The stage of disease at diagnosis was assessed according to the modification system of Musshoff and Schmidt-Vollmer after evaluation of clinical, surgical and pathologic findings in each case (Musshoff and Schmidt-Vollmer 1975); the subclassifications respectively denote involvement of lymph nodes contiguous with (IIE-1) or not contiguous with (IIE-2) the primary site.

At the completion of chemotherapy, patients were restaged with the investigations described above to determine disease status according to WHO criteria (WHO 1979). Survival curves were calculated from the date of surgery until the date of last follow-up or date of death, and the survival curves were prepared using the Kaplan-Meier method (Kaplan and Meier 1958). Z-test was used to evaluate differences in survival curves. Univariate comparisons were performed using the Fisher's exact test (Wilcoxon 1945).

Table 3. Characteristics of the patients

Features	Treatment modality			Total (n=40)
	Operation alone (n=16)	With adjuvant radiotherapy (n=7)	With adjuvant chemoradiotherapy (n=17)	
Age (year)				
median	57.6	8.5	43.5	49.1
range	23-74	26-63	15-72	15-74
M:F	11:5	4:3	13:4	7:3
Site				
stomach	8	7	8	23
intestine	8	0	9	17
Stage				
IE	7	5	7	19
IIE-1	1	1	3	5
IIE-2	8	1	7	16
Histology				
WDLL	5	1	4	10
PDLL	4	3	2	9
DM	2	0	0	2
DH	5	3	11	19
Grade				
low	5	1	5	11
intermediate	9	5	10	24
high	2	1	2	5
Follow-up duration (week)				
median	7.1	43.5	28.5	16.8
range	1-40+	1+-102+	2+-68+	1+-102+

WDLL: well-differentiated lymphocytic lymphoma, PDLL: poorly-differentiated lymphocytic lymphoma, DM: diffuse mixed lymphocytic and histiocytic lymphoma, DH: diffuse histiocytic lymphoma

RESULTS

The characteristics of the forty patients with localized gastrointestinal lymphoma treated with surgery and postoperative adjuvant therapy are shown in Table 3. There were twenty-three patients of primary gastric lymphoma, and seventeen patients of primary intestinal lymphoma. In intestinal lymphoma, nine patients were localized in the small bowel (ileum 8, jejunum 1), three patients in the large bowel (cecum), and five patients were in the small and large bowel (ileocecal). The median age was 49.1 years (range, 15-74 years; male: female ratio, 7:3). Seven of the twenty-three patients with primary gastric lymphoma received total gastrectomy and sixteen patients received subtotal gastrectomy. Nine patients with only small bowel lesion received partial small bowel resection, and eight patients with large bowel lymphoma received hemicolectomy. According to the Arbor scheme, nineteen patients had stage IE and twenty-one patients had stage IIE disease. Stage IE disease was more common in stomach lymphoma, while stage IIE disease was more common in intestinal lymphoma ($p<0.01$). Stage IIE disease was subdivided according to the modification proposed by Musshoff: perigastric or mesenteric (in intestinal tumors) nodal involvement by tumors was IIE-1; and positive abdominal lymph nodes not contiguous with the site of the gastrointestinal tract were stage IIE-2. Among twenty-one stage IIE patients, five patients were stage IIE-1, and sixteen patients were stage IIE-2. Stage IIE-2 disease was more prevalent in intestinal lymphoma ($p<0.05$). Ten patients had diffuse well differentiated lymphocytic lymphoma, nine diffuse poorly differentiated

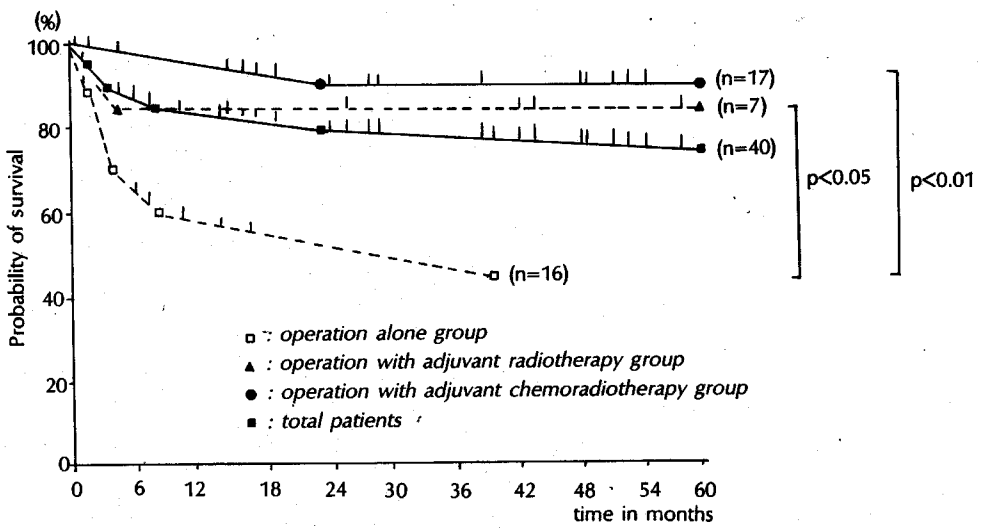

Fig. 1. A comparison of the survival of patients according to each treatment modality.

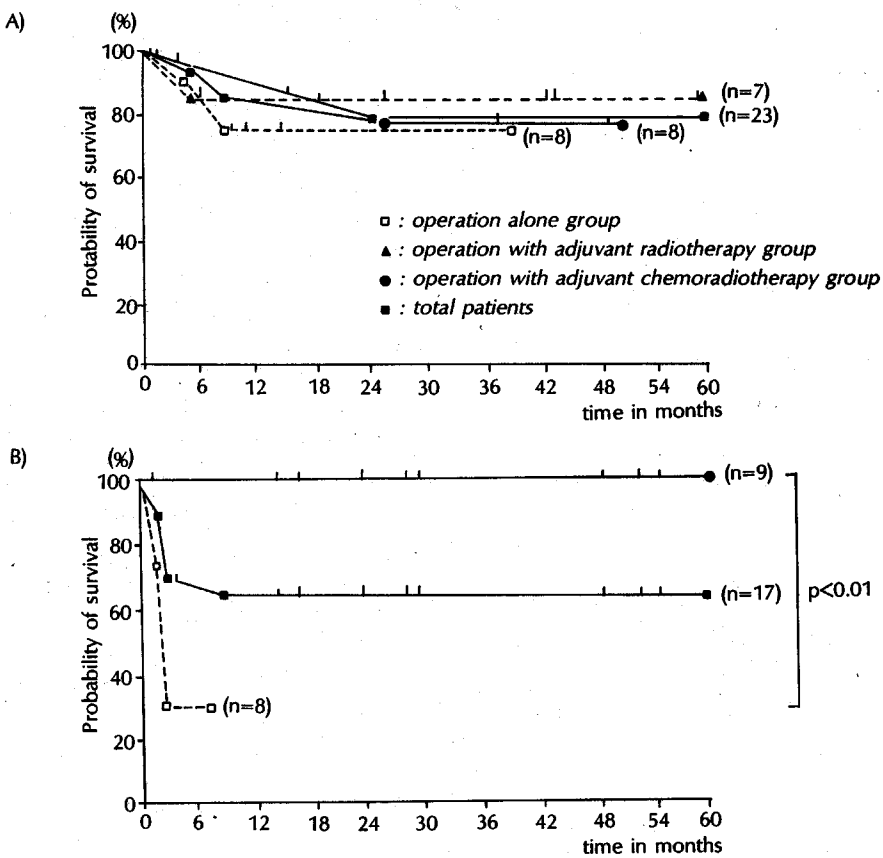

Fig. 2. A comparison of the survival of patients according to each treatment modality in stomach & intestine. A) stomach B) intestine

lymphocytic lymphoma, two diffuse mixed lymphocytic and histiocytic lymphoma, and nineteen diffuse histiocytic lymphoma. Intermediate or high grade tumors by NCI criteria accounted for 72.5% of lesions (29 of 40) (Table 3).

All patients were available for analysis and have been followed for a median of 17 months (range 1–102+months). The median survival has not yet been reached, but the five year survival for the entire group of patients was 71.0%. The 40 month survival rate of the operation alone modality group was 42.7%, which was significantly lower than the survival rates of 83.3% in the postoperative adjuvant radiotherapy group and 90.0% in the postoperative adjuvant chemoradiotherapy group at five years ($p<0.05$, $p<0.01$ each) (Fig. 1). In primary gastric lymphoma, the overall five year survival for patients in all treatment categories was 76.4%. The survival of the patients who underwent only gastrectomy was 69.3%, and was 84.6% with adjuvant radiotherapy and 75.0% with adjuvant chemoradiotherapy. No statistical differences were found yet between these treatment modalities. However, in primary intestinal lymphoma, a meaningful difference was found between the operation alone modality group and the multimodality group. The overall survival for the patients in all treatment categories was 62.4%. The survival of the segmentectomy or hemicolectomy group was only 28.6% at five years, while with the addition of adjuvant chemoradiotherapy, the survival was increased to 100% at five years ($p<0.01$) (Fig. 2).

The effect of different treaments on survival was shown separately for patients with stage IE and stage IIE diseases. In general, the results for those with stage IE and stage IIE-1 diseases were satisfactory, whereas results for the stage IIE-2 were poor, especially in patients with operation alone. For the 8 patients with stage IIE-2 disease who had a gastrectomy or hemicolectomy without adjuvant treament, the five year survival was only 16.7%. The 7 patients who received postoperative adjuvant chemoradiotherapy in this group showed 100% survival at five years

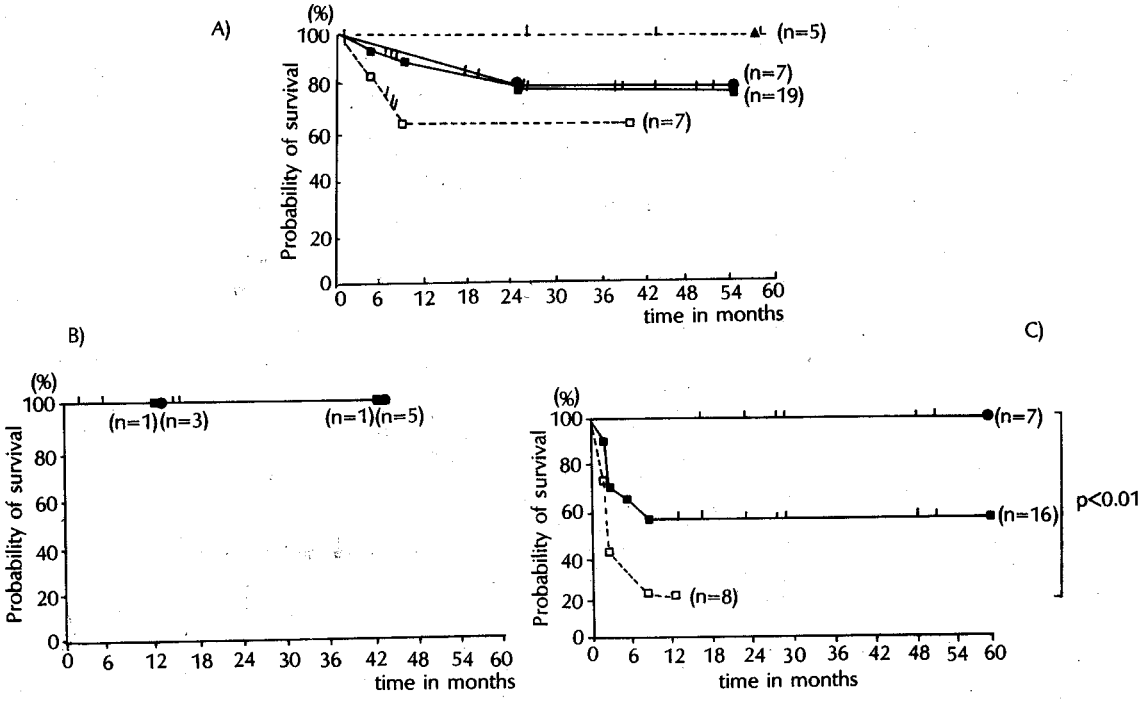

Fig. 3. *A comparison of the survival of patients according to each treatment modality in stage IE & IIE.*
A) stage IE B) stage IIE-1 C) stage IIE-2
□: operation alone group
▲: operation with adjuvant radiotherapy group
●: operation with adjuvant chemoradiotherapy group
■: total patients

(p<0.01) (Fig. 3). The effect of different treatments on survival was also shown separately for different histopathologies in Rappaport classification. Survivals for the 11 well differentiated lymphocytic lymphomas was 90.9%. Five of them received operation alone, and the five year survival was 80%, which was increased to 100% in another 4 patients with addition of chemoradiotherapy. One patient received adjuvant radiotherapy alone and he is still alive in a complete remission state for 102 months. With operation alone, the survivals of poorly differentiated lymphocytic lymphoma and diffuse histiocytic lymphoma were 33.0% at five months and ten months respectively. With the addition of adjuvant radiotherapy, the survivals were increased to 100% and 67.0%, and were increased up to 100% each (p<0.05, p<0.01 each) with adjuvant chemoradiotherapy (Fig. 4). The effect of different treatments on survival was also shown separately for assigned grades in accordance with the NCI Working formulation. The results for those with low grade disease were satisfactory, whereas results for those with intermediate and high grades were poor. In low grade disease, the five year survival was 80% with operation alone, and was increased to 100% with adjuvant radiotherapy and chemoradiotherapy. In intermediate grade disease, treatment selection strongly influenced survival. With operation alone, the five year survival was just 16.0%, which was increased up to 100% with adjuvant treatment arms (p<0.01 each). The result was similar in the high grade group. With operation alone, the survival was 50%, which was increased up to 100% at five years with adjuvant treatments (Fig. 5).

Among forty patients, relapse occured in 10 patients (25%) within 2 years of therapy. In adjuvant treatmetn groups, 1 of 7 (14.3%) in the adjuvant

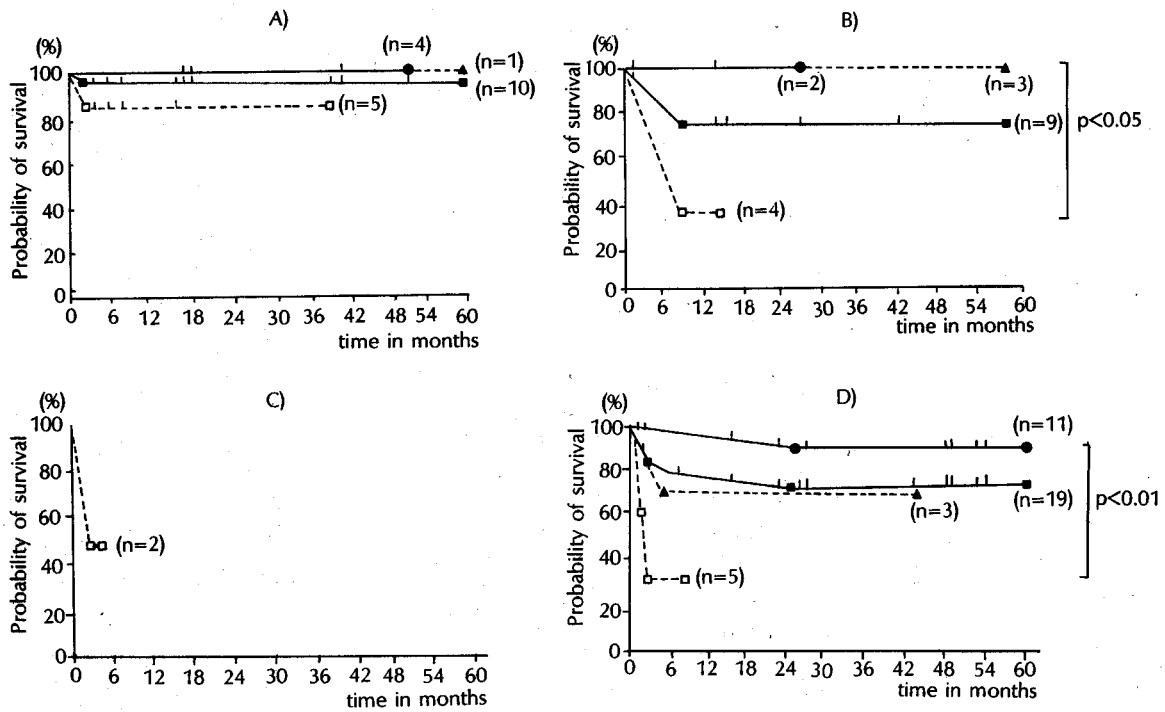

Fig. 4. A comparison of the survival of patients according to each treatment modality in each histopathology by Rappaport.
A) well-differentiated lymphocytic lymphoma
B) poorly-differentiated lymphocytic lymphoma
C) mixed lymphocytic and histiocytic lymphoma
D) diffuse histiocytic lymphoma
□: operation alone group
▲: operation with adjuvant radiotherapy group
●: operation with adjuvant chemoradiotherapy group
■: total patients

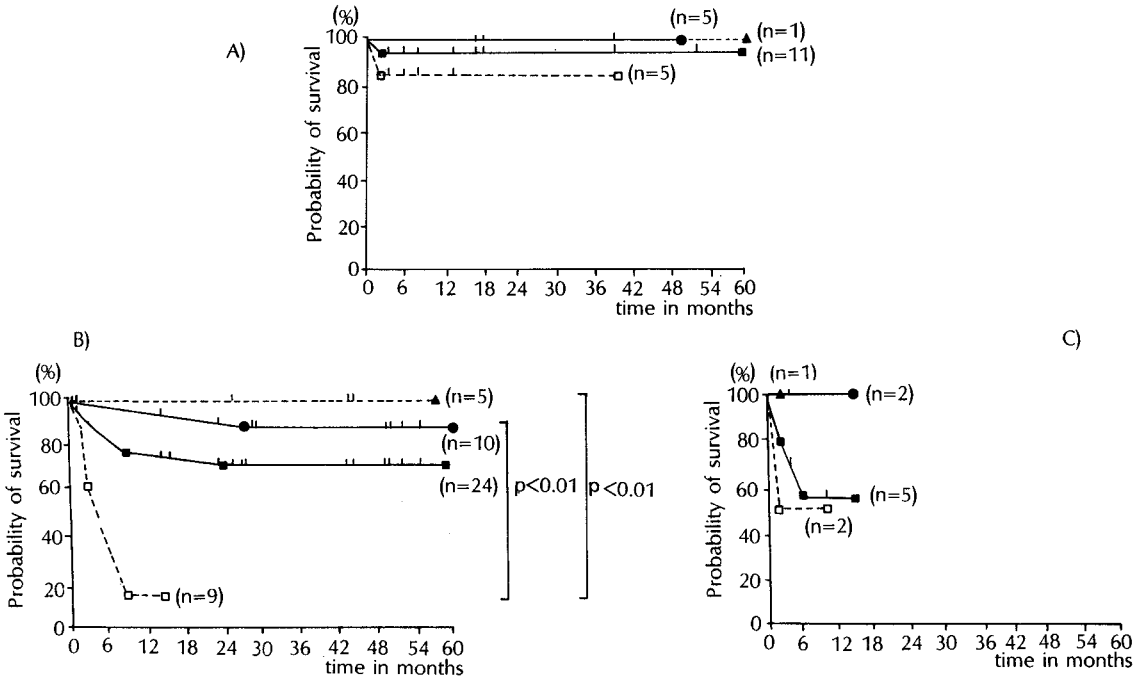

Fig. 5. *A comparison of the survival of patients according to each treatment modality in each grade by NCI working formulation.*
A) low grade B) intermediate grade C) high grade
□: operation alone group
▲: operation with adjuvant radiotherapy group
●: operation with adjuvant chemoradiotherapy group
■: total patients

Table 4. Relapse pattern in each treatment modality

	Treatment modality			Total (n=40)
	Operation alone (n=16)	With adjuvant radiotherapy (n=7)	With dajuvant chemoradiotherapy (n=17)	
Local relapse (%)	3 (19)	1 (14)*	0	4 (10)
Distant relapse (%)	5 (31)	1 (14)*	1 (6)	7 (18)
lung	1	–	–	1
liver	3	–	1	4
bone marrow	1	–	–	1
lymph node	–	1	–	1
Interval between operation and relapse (months)	3	3	23	
Disease-related death	6 (38)	1 (14)	1 (6)	8 (20)
Cause of death				
progression	4	1	1	6
bleeding	2	–	–	2

* Simultaneous local and distant failure

Table 5. Complications in each treatment modality

Complications	Treatment modality		
	Operation alone (n=16) (%)	With adjuvant radiotherapy (n=7) (%)	With adjuvant chemoradiotherapy (n=17) (%)
Treatment-related death	1 (6)	–	–
Anorexia	–	7 (100)	17 (100)
Nausea & Vomiting	–	7 (100)	17 (100)
Alopecia	–	7 (100)	17 (100)
Bowel habit change	–	7 (100)	17 (100)
Mucositis	–	–	15 (88)
Leukopenia (<1000/m^3)	–	–	9 (53)
Anemia (<10g/l)	–	–	9 (53)
Infection	–	–	5 (33)
Hematuria	–	–	2 (13)
Constipation	–	–	2 (13)
Paresthesia	–	–	1 (7)

radiotherapy group relapsed from the primary site and the distant area lymph nodes, and 1 of 17 (5.9%) in the adjuvant chemoradiotherapy group relapsed from the liver. Eight of 16 (43.8%) patients treated with operation alone relapsed; 3 from the primary site and 5 from the distant area (1 lung; 3 liver; 1 bone marrow). All 3 primary site relapsed cases and 3 of 5 distant site relapsed cases were stage IIE-2 diseases. Nine patients died during the follow-up period; 1 from multiple organ failure, and 8 from disease-association (Table 4). The main causes of death were liver failure due to disease progression in 6 patients, and intractable bleeding from the primary site relapse in 2 patients. Early mortality arising from local treatment-related complications was observed in one patient (5%). Mild gastrointestinal upset with nausea, vomiting and diarrhea were common during abdominal irradiation and chemotherapy, but were easily managed in the majority of the patients (Table 5).

DISCUSSION

In systemic malignant lymphoma, involvement of the gastrointestinal tract is common and is observed in about 50% of many necropsy series (Ehrlich *et al.* 1968). In contrast to this fact, primary gastrointestinal lymphomas are rare neoplasms that represent only 1 to 4% of all gastrointestinal tract malignancies (Loehr *et al.* 1969). However, the gastrointestinal tract is the most common extra-nodal location for the development of non-Hodgkin's lymphoma (Paryani *et al.* 1983). The anatomic distribution of the primary gastrointestinal lymphomas in the current series was 58% in the stomach, 22% in the small intestine, 13% in the ileocecal region, and 7% in the ascending colon, consistent with that observed in previous reports (Aozasa *et al.* 1988).

The mainstay of treatment of non-Hodgkin's G-I tract lymphoma during earlier periods was a surgical resection. The importance of this treatment is documented if postoperative radiotherapy is planned, due to the increased incidence of hemorrhage and perforation. During the 1960s, the standard treatment modality in localized G-I tract lymphoma was surgery alone or surgery with adjuvant radiotherapy in Korea (suh *et al.* 1966; Suh *et al.* 1968). These reports did not compare the survivals due to the short follow-up duration, and the small number of patients. During the early 1980s, sporadic reports reviewed the survivals of localized G-I tract lymphoma with stages (Chung *et al.* 1982; Joo *et al.* 1983, Joo *et al.* 1985). Joo *et al.* (1983) reported a 71% 3 year survival rate in 7 patients, but they did not compare the results with treatment modalities also. Recently, adjuvant chemotherapy was tried, especially in stage II lymphoma after surgery. Park *et al.* (1986) reported 17 cases of G-I tract lymphoma with different treatment modalities. They treated two patients with surgery alone, three patients with surgery and adjuvant radiotherapy, and twelve patients with surgery and adjuvant chemotherapy. Three year and five year sur-

vivals in stage I were 100% and 83.3% respectively. But their results for 5 year survival of stage I and II decreased to 46.2%, suggesting a more adjuvant treatment in stage II disease. Unfortunately, they did not compare the result according to the treatment modalities. Our results showed that patients who underwent operation alone had the lowest five year survivals compared with the groups undergoing surgery and postoperative radiotherapy and chemoradiotherapy. The five year survival rate of 69.3% achieved in our study with operation alone compares favorably with that of other series (Shimm *et al.* 1983; Joo *et al.* 1983; Shiu *et al.* 1986). Although significant statistical results are not achieved yet, the survival was increased to 84.6% and 75% at five year with adjuvant radiotherapy and chemoradiotherapy respectively. Similar results were obtained by Jones *et al.* (1988), and by an Australian group (Stewart and Hess 1987). They had conducted a prospective pilot study with postoperative adjuvant chemotherapy in 18 patients. Their actuarial survival at a median follow-up of 41 months was 99% (Stewart and Hess 1987). Their and our results suggested the need for adjuvant treatment in patients with gastric lymphoma after resection, especially in patients with locally advanced disease. The significance of postoperative adjuvant treatment in locally advanced cases, although completely resected, appeared more definitely in intestinal lymphomas of our series. The five year survival in the operation alone group was only 28.6%, which was increased to 100% with adjuvant chemoradiotherapy ($p<0.01$). Therefore, it appears that adjuvant chemoradiotherapy improves survival, in that it probably sterilizes the postoperative field of any residual microscopic disease.

It is well known that survival in gastrointestinal lymphoma is influenced by the stage of disease at the time of diagnosis. So, in staging the primary gastrintestinal lymphoma, all efforts should be directed to rule out the presence of disseminated disease which would tend to preclude the need for major surgical intervention. However, the Ann Arbor staging system appears suboptimal when applied to individuals for diagnosing primary gastrointestinal lymphomas because it does not distinguish the involvement of regional and mesenteric nodes from that of retroperitoneal nodes. We used the Musshoff staging system which seems to be the most functional because it subdivides stage IIE into stage IIE-1 (contiguous) and stage IIE-2 (non-contiguous). In our series, tumor spread to regional or distant abdominal lymph nodes, which was classified as stage IIE, was the major cause of a pronounced tendency for more advanced disease among intestinal lymphoma patients ($p<0.01$). Similar findings were reported by Cheon *et al.* (1988). Although this disparate distribution in anatomic stage reflects the unavoidable bias of the study, and may have contributed to the inferior results observed in the intestinal lymphoma patients group, this early lymphatic spread may be one of the reasons for poorer prognosis than that of gastric lymphoma. Some other researchers (Shepherd *et al.* 1988) did not agree with this conclusion.

Surgical resection alone had appeared to be curative in essentially all patients having a stage IE disease. In the 1960s, radical surgical procedures were performed. However, due to the high operative mortality and local recurrence rate, and the development of adjuvant postoperative radiotherapy, limited surgery is now recommended. With the improvement of surgical techniques, the operative mortality has been reduced to 9.5 to 16% (Weingrad *et al.* 1982; Maor *et al.* 1984). The other important factor of preliminary surgery is the prevention of perforation and hemorrhage. This point is argued by Herrmann *et al.* (1983), Gary *et al.* (1982), and Maor *et al.* (1984). They proposed a combination of chemotherapy alternated with local radiotherapy, and reserved surgery only for complications and for tumors which failed to respond to initial chemotherapy. But the small number of patients studied does not allow for comparison with a surgical series, nor can any conclusion be reached concerning the advisability of this approach. Recently with the postoperative adjuvant radiotherapy, the cure rate of stage IE disease has increased to approximately 75% (Bush *et al.* 1977; Maor *et al.* 1984). However, the choice of the type of adjuvant therapy after complete resection of stage IE or IIE diseases was debatable, because available data suggests that either abdominal irradiation or adjuvant chemotherapy can be used with about equal success rates after surgical resection (Shiu *et al.* 1986), and randomized studies are not available. Currently, Maor *et al.* (1984) reported promising results in patients treated in a multimodality program consisting of chemotherapy and radiotherapy in the management of resected as well as unresected stage IE and IIE disease states. And Shiu *et al.* (1986) reported significantly improved results for stage IE and IIE resectable tumors over those of similar tumors treated in the 1950s and 1960s. The estimated five year survival rate after treatment was 95% and 78% respectively for stage IE and stage IIE in this group. Another important point of the adjuvant radiotherapy program is that the incidence of disseminated failure has been increased after the development of postoperative radiotherapy (We-

ingrad *et al.* 1982; Shimm *et al.* 1983). So in order to avoid early relapse, and with a special consideration of the ability of chemotherapy to produce long-term remission and cure in diffuse histiocytic lymphoma, an early start of chemotherapy is now recommended, followed by radiotherapy (Nissen *et al.* 1983) in a multimodality program.

To decrease local and systemic relapse, we delivered chemotherapeutic agents as soon as possible, followed by radiotherapy and maintenance chemotherapy, using the sandwich technique after complete removal of the primary tumor. Initially, the chemotherapeutic regimen usually recommended for lymphoma was C-MOPP (McKelvey *et al.* 1976; Fisher *et al.* 1977). With the use of the adriamycin-containing combination regimen, a high proportion of durable, complete remissions can be achieved (Jones *et al.* 1979). Our patients were given chemotherapy with a 4 drug regimen based on adramycin (ACOP). In our series, following pathologic staging, there were 19 patients with stage IE and 21 patients with stage IIE disease. The overall survival of stage IE was 79.1%. But the survival of the operation alone group was just 55.6%, which was increased with adjuvant treatments. Although a statistically significant superiority was not yet obtained between radiotherapy and chemoradiotherapy, these results encouraged us to consider adjuvant treatment. In stage IIE-1 disease, there were only 5 patients; 1 received operation alone, 1 received adjuvant radiotherapy and 3 received adjuvant chemoradiotherapy. All of thse five patients are still alive in a complete remission state (2+ - 43+ months). In these low stage diseases (stage I to IIE-1), we could not find any superiority between the two adjuvant arms till now due to the small number of patients and short follow-up duration. Shimm *et al.* (1983) concluded that overall survival was not affected by radiation and noted that the majority of recurrences were distant, indicating a need for effective systemic chemotherapy. In stage IIE-2 disease, the situation is very different. One patient received adjuvant radiotherapy, but local and distant failure occurred. Seven patients received operation alone, and 7 patients received adjuvant chemoradiotherapy. No recurrence occured in this adjuvant chemoradiotherapy group (16+ - 68+ months). The survivals also were statistically different between the two treatment modalities (16.7% vs 100%), suggesting the important role of adjuvant treatment in these locally advanced groups.

There are conflicting reports concerning the importance of histologic subtype in the determination of long-term survival (Lewin *et al.* 1978; Herrmann *et al.* 1980; Shimm *et al.* 1983). The results generally revealed that the histologic classification was not significant for prognosis (Gospodarowicz *et al.* 1982). However, a more recent review has suggested a correlation between the histologic subtypes and survival (Filippa. *et al.* 1983; Dragosics *et al.* 1985), and furthermore, Weingrad *et al.* (1982) and Aozasa *et al.* (1985) reported that the Kiel classification was prognostically significant. In a statistical review, the histologic type of the lymphomas was only a minor determinant of prognosis as shown by multivariate analysis, which included stage, surgical resection, and treatment (Shepherd *et al.* 1988). We compared the results of the three treatment modalities in the same histopathology group according to Rappaport classification and same grade assigned by the NCI Working Formulation. Although poor prognosis was found in poorly differentiated lymphocytic lymphoma, diffuse histiocytic lymphoma, and the intermediate to high grade group in our series, it is difficult for us to comment on the influence of histology in our small number of patients in each subgroup. In each histopathology group, the survival was varied according to the selection of the treatment modality. In the low grade group and the well differentiated lymphocytic lymphoma group, the survival rates showed 80% each, and were increased to 100% with the addition of the adjuvant treatments, which was not statistically significant yet. In aggressive-histology lymphomas, in contrast to the above findings, significant increases of survival were observed with the adjuvant treatments, and this finding was more evident in diffuse histiocytic lymphomas.

As described before, the major advantage of adjuvant chemotherapy is the prevention of systemic relapse. With only adjuvant radiotherapy, Weingrad *et al.* (1982) reported a 68% recurrence rate outside the primary treatment field, and 60% outside the abdomen. Opposite to this report, Maor *et al.* (1984) reorted only one of 13 patients relapsed following treatment with adjuvant chemoradiotherapy. Similar reports were found in this study; 1 local and distant failure from the radiotherapy only group with initial stage IIE-2, 1 distant failure from the chemoradiotherapy group with initial stage IE, 3 local failures with initial stage IIE-2 and 5 distant failures from the operation alone group. These results suggest the importance of systemic failure in controlling the disease and the importance of the role of chemotherapy in resolving the systemic relapse and increasing the disease free survival. All relapsed cases occurred within two years after operation.

Even if the multimodality treatment has yielded higher cure rates, its morbidity requires special con-

sideration, especially for elderly patients. Therefore, selection of those patients who would benefit most from a combined modality approach is essential. And there is some question about the necessity of adjuvant therapy in stage IE gastric lymphoma limited to the gastric mucosa and submucosa. We treated 14 patients limited to the mucosa and submocusa, and 3 patients (21%) relapsed from the liver; 2 patients with operation alone at 2 and 6 months each, and 1 patient with adjuvant chemoradiotherapy at 23 months after operation. Recognizing the limitations of a retrospective study and patient number, these issues must be evaluated in the prospective application. Over the years the operative mortality was decreased from 18% (Naqvi *et al.* 1969) to 9.5% (Weingrad *et al.* 1982). In our study the improved survival rates have been achieved with low surgical operative mortality (2.5%). Shiu *et al.* (1986) reported no operative mortality in their study. They reported an experience of one esophageal strictu;re, one small bowel obstruction, 3 herpes zoster infections, and 3 malabsorptions in 42 patients. Also they reported mild gastrointestinal upsets with nausea, vomiting, and diarrhea in almost all patients, which were easily manageable. In our study, the side effects of treatment, such as gastrointestinal upset, bone marrow depression and infection, have been manageable and reversible in all the patients and chemotherapy was administred without dose reduction. No additive effects of complications and adjuvant treatment-related deaths were observed during the adjuvant chemoradiotherapy period.

In conclusion, although our data strongly suggest the significance of postoperative adjuvant treatment, it is not conclusively determined yet whether or not the chemoradiotherapy is superior to the radiotherapy alone or not as an adjuvant treatment.

REFERENCES

Aozasa K, Tsujimoto M, Sakurai M: Non-Hodgkin's lymphoma in Osaka, Japan. *Eur J Cancer Clin Oncol 21:487, 1988*

Bush RS, Gospodarowicz M, Sturgeon J, Alison R: Radiation therapy of localized non-Hodgkin's lymphoma. *Cancer Treat Rep 61:1129, 1977*

Cabanillas F, Bodey GP, Freireich EJ: Management with chemotherapy only of stage I and II malignant lymphoma of aggressive histologic types. *Cancer 46:2356, 1980*

Cheon JW, Song HS, Kim IH: A clinical study of gastrointestinal lymphomas. *Kor J Int Med 34:681, 1988*

Chung DJ, Lee KU, Kim JP: Primary gastrointestinal lymphoma. *J Kor Surg Socie 24:310, 1982*

Dawson IMP, Comes JS, Morson BS: Malignant tumors of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. *Br J Surg 49:80, 1961*

Dragosics B, Bauer P, Radaszkiewicz T: Primary gastrointestinal non-Hodgkin's lymphoma; a retrospective clinicopathologic study of 150 cases. *Cancer 55:1060, 1985*

Ehrlich AN, Stadler G, Gellar W: Gastrointestinal manifestations of malignant lymphoma. *Gastroenterol 54:1115, 1968*

Fillipa DA, Liberman PM, Weingrad DN: Primary lymphomas of the gastrointestinal tract: Analysis of prognostic factors with emphasis on histological types. *Am J Surg 7:363, 1983*

Fisher RI, DeVita VJ Jr., Johnson BC: Prognostic factors for advanced diffuse histiocytic lymphoma following treatment with combination chemotherapy. *Am J Med 63:177, 1977*

Freeman C, Berg JW, Cutler SJ: Occurrence and prognosis of extranodal lymphomas. *Cancer 29:252, 1972*

Gary GM, Rosenberg SA, Cooper AD, Gregory PB, Stein DT, Herzenberg H: Lymphomas involving the gastrointestinal tract. *Gastroenterol 82:143, 1982*

Gospodarowicz MK, Bush RS, Brown TC, Chua T: Curability of gastrointestinal lymphoma with combined surgery and radiation. *Int J Rad Oncol 9:3, 1982*

Herrmann R, Panahon AM, Barms MP: Gastrointestinal involvement in non-Hodgkin's lymphomas. *Cancer 46:125, 1980*

Jones RE, Willis S, Innes DJ, Wanebo HJ: Primary gastric lymphoma; Problems in staging and management. *Am J Surg 155:118, 1988*

Jones SE, Grozea PW, Metz EN: Superiority of adriamycin-containing combination chemotherapy in the treatment of diffuse lymphoma. A Southwest Oncology Group Study. *Cancer 43:417, 1979*

Joo KK, Yoon YK, Joo HZ: Primary malignant lymphoma of the gastrointestinal tract. *J Kor Cancer Res 17:245, 1985*

Joo SH, Yoon JW, Hahn JS, Ko YW, Park IS, Choi HJ, Kim TS: Primary gastrointestinal lymphoma. *Kor J Hematol 18:191, 1983*

Kaplan EL, Meier P: Non-parametric estimation from incomplete observation. *J Am Statist Assoc 53:457, 1958*

Kim TY, Lee HS, Paik NW: Clinical study on primary gastrointestinal lymphoma. *J Kor Surg Socie 34:590, 1988*

Lewin KJ, Ranchod M, Dorfman RF: Lymphomas of the gastrointestinal tract: A study of 117 cases presenting with gastrointestinal disease. *Cancer 42:693, 1978*

Loehr WJ, Mujahed Z, Zahn FD: Primary lymphoma of the gastrointestinal tract; a review of 100 cases. *Ann Surg 170:232, 1969*

Maor MH, Maddux B, Osborne BM, Fuller LM, Sullivan JA, Nelson RS, Martin RG, Libshifz HI, Velasquez WS, Bennett RW: Stage IE and IIE non-Hodgkin's lymphomas of

the stomach; Comparison of treatment modalities. *Cancer 54:2330, 1984*

McKelvey EM, Gottlieb JA, Wilson HZ: Hydroxydaunomycin combination chemotherapy in malignant lymphoma. *Cancer 38:1484, 1976*

Musshoff K, Schmidt-Vollmer H: Prognosis of non-Hodgkin's lymphoma with special emphasis on the staging classification. *Z Krebsforsch 83:323, 1975*

National Cancer Institute sponsored study of classification of non-Hodgkin's lymphoma, summary of a Working Formulation for clinical use: The non-Hodgkin's lymphoma pathologic classification projects. *Cancer 49:2112, 1982*

Naqvi MS, Burrows L, Kark AE: Lymphoma of the gastrointestinal tract; Prognostic guides based on 162 cases. *Ann Surg 170:221, 1969*

Nissen NI, Ersbill J, Hansen HS, Walbon-Jorgensen S, Pedersen-Bjergaard J, Hansen MM, Rygard J: A randomized study of radiotherapy versus radiotherapy plus chemotherapy in stage I-II non-Hodgkin's lymphomas. *Cancer 52:1, 1983*

Park BK, Yang SH, Kim IY, Kim SS, Koo JY, Park BC: Primary gastrointestinal lymphoma. *Kor J Gastroenterol 18:123, 1986*

Paryani S, Hoppe RT, Burke JS: Extralymphatic involvement in diffuse non-Hodgkin's lymphoma. *J Clin Oncol 1:682, 1983*

Rappaport H, Winter WJ, Hicks FB: Follicular lymphoma: A reevaluation of its position in the scheme of maligant lymphomas, based on a survey of 253 cases. *Cancer 9:792, 1956*

Shepherd FA, Evans WK, Kutas G, Yan JC, Dang P, Scott JG, Farquharson HN, Francombe WH, Bailey D, Barker MA: Chemotherapy following surgery for stage IE and IIE non-Hodgkin's lymphoma of the gastrointestinal tract. *J Clin Oncol 6:253, 1988*

Shimm DS, Dosoretz DE, Anderson T, Linggoud RM, Harris NL, Wang CC: Primary gastric lymphoma; an analysis with emphasis on prognostic factors and radiation therapy. *Cancer 52:2044, 1983*

Shiu MH, Nisce LE, Pinna A, Straus DJ, Tome M, Fillpa DA, Lee BJ: Recent results of multimodal therapy of gastric lymphoma. *Cancer 58:1389, 1986*

Stewart FM, Hess CE: *Malignant lymphomas.* In: Thomp OA, Bithell TC, Hess CE, eds. *Fundamentals of Clinical Hematology,* 5th ed. Philadelphia, WB Saunders, *1987, 616-719*

Suh HS, Huh CH, Lee TH, Whang KC: Primary malignant lymphoma of the gastrointestinal tract. *J Kor surg Socie 8:239, 1966*

Suh JH, Kwak JY, Chung DJ, Kang HS: Clinical review of primary malignant lymphoma of the gastrointestinal tract. *J Kor Surg Socie 10:483, 1968*

Weingrad DW, Decosse JJ, Sherlock P, Straus D, Lieberman PH, Filippa DA: Primary gastrointestinal lymphoma; A 30-year review. *Cancer 49:1258, 1982*

WHO handbook for reporting results of cancer treatment. World Health Organization, Geneva, *1979*

Wilcoxon F: Individual comparison by ranking methods. *Biometr 1:50, 1945*