Combined Surgery and Radiotherapy in the Stage I and II Primary Gastrointestinal Non-Hodgkin's Lymphomas

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Thirty eight patients with stage I and II primary gastrointestinal non-Hodgkin's lymphoma were treated in the Department of Therapeutic Radiology, Seoul National University Hospital between 1979 and 1984.

There were 6 systemic disseminations during radiotherapy, and the overall failure rate were 31 % in the cases with tumor bulk less than 5 cm in diameter before radiotherapy and 75% in the cases with tumor bulk greater than 5 cm in diameter ($p<0.05$).

The overall 5 year survival rate were 69.2% in 28 patients who completed radiotherpay and 72 % in 24 patients with tumor bulk less than 5 cm in diameter (small or no tumor bulk). The 5 year disease free survival rate were 71% in cases with tumor bulk less than 5 cm in diameter and 25 % in cases with tumor bulk greater than 5 cm in diameter ($p<0.01$). But the intitial stage was not related with treatment result in all cases or subgroups of cases.

Thus the cases with small or no tumor bulk were shown to be curable with combined surgery and postoperative radiotherapy, but for the control of the cases with large tumor bulk that had a guarded prognosis combined radiotherapy and chemotherapy should be tried.

Key Words: Primary gastrointestinal non-Hodgkin's lymphoma, Radiotherapy, Tumor bulk.

INTRODUCTION

The primary gastrointestinal non-Hodgkin's lymphoma is the most common extranodal NHL[1~3].

Operation has the important role in the management of GI NHL by histologic diagnosis, accurate staging, and tumor resection. And so more meaningful prognostication and therapeutic decisions can be made[4]. But when surgery was the sole method of treatment, result was not so good that 5 year survival rate was in the range of 15% to 55 %[5,6].

Postoperative radiotherapy markedly improved the treatment result especially in the cases with residual tumor[1,5~9].

We analyzed the treatment result of GI NHL cases registered in the Seoul National University Hospital. The patterns of relapse and survival data were evaluated in association with pre-radiotherapy tumor bulk.

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MATERIALS AND METHODS

From 1979 to 1984, 38 patients of primary gastrointestinal NHL stage I or II were treated with combined surgery and postoperative radiotherapy in the Department of Therapeutic Radiology, Seoul National University Hospital.

Twenty two patients were male and 16 were female. The age ranged from 18 to 74. The sixties were most common and 71% of the patients were in their 40's to 60's. And 2 patients were combined with the second malignant tumors, one with papillary carcinoma of the thyroid and one with adenocarcinoma of the jejunum.

Tissue diagnosis was obtained in all patients by endoscopic biopsy or laparotomy and classified by Rappaport system. Careful history and physical examination, complete blood count, liver and kidney function tests, liver scan, bone scan, and bone marrow aspiration and biopsy were done as basal

work-up's. And then the patients were staged according to the Ann Arbor classification using laparotomy findings and pre- or post-operative evaluation.

Before radiotherapy, abdominal CT was done for the evaluation of residual tumor but UGI, small bowel series, and colon studies were not performed again. The tumor bulk was classified into 3 groups before radiotherapy by physical and CT findings. When the resection was complete and there was no gross or microscopic residual mass, the tumor status was defined as 'no bulk'. Patients with microscopic tumor at surgical resection margin or gross tumor mass less than 5 cm in diameter were defined as 'small bulk' and cases with gross tumor mass greater than 5 cm were defined as 'large bulk'. Patient characteristics are shown according to the tumor bulk in Table 1.

Rapid progession of the disease at 2 weeks to 7 months after complete resection made 5 patients (4 with stage II, 1 with stage I) be in large bulk group. Other 2 cases, otherwise be in no bulk group, were classified as small and large bulk each in the absence of clinical sign just after complete resection by pre-radiotherapy abdominal CT (Table 2).

After operation all patients were treated with megavoltage radiation. All patients with primary bowel NHL and most of primary gastric NHL cases took radiotherapy as followes; 2,000 cGy to whole abdomen, 100 cGy per fraction, 5 fractions a week, was followed by 2,000 to 3,000 cGy boost to the primary or residual site, 180 cGy per fraction, 5 fractions a week. And posterior kidney shielding was applied at the dose of 1,000 cGy when the radiation field encompassed one or both kidneys. The minimal dose of complete treatment was 2,000 cGy in cases with no bulk and 4,000 cGy in small or large bulk. Three patients with no bulk received 2,000 to 3,000 cGy with above technique. And 4 patients of primary gastric NHL with no bulk were delivered with 4,000 cGy or more by involved field encompassing the left upper quadrant of the abdomen. Parallel opposed AP: PA ports wre used and the both fields were treated everday.

In relapse analysis, involvement of bone marrow or liver was regarded as systemic dissemination. And the overall or disease free survival rate was calculated with life table actuarial survival[10] measured from the operation date in cases with no bulk and from the first day of radiotherapy in cases with small or large bulk. And the patients whose cause of death were unknown are not censored but considered to have relapsed and died of GI NHL. Significance between survival rate was determined by log rank test[11].

Table 1. Distribution of the Tumor Bulk by Stages, Histology, and Sites

	No bulk	Small bulk	Large bulk	Total
Stage				
I	10	–	1	11
II	14	5	8	17
Histology				
NPDL	–	1	–	1
NH	–	1	–	1
DPDL	12	1	4	17
DH	11	2	4	17
DM	1	–	–	1
IB *	–	–	1	1
Site				
Stomach	12	2	1	15
Bowel	12	3	7	22
Mesentery	–	–	1	1
Total	24	5	9	38

Note ; * ; immunoblastic

RESULT

Of all 38 patients, 28 patients completed radiotherapy. Four patients gave up further treatment without progression of disease of their own will and systemic dissemination was the cause in other 6 patients, all of them were initially in stage II (Table 3). All relapses occurred within 2 years after completion of radiotherapy.

In cases with no bulk, there were 2 cases of systemic relapse during radiotherapy and 4 relapsed at 1, 2, 5, 22 months after completion of

Table 2. Distribution of Tumor Bulk by the Extent of Operation

	Tumor bulk			Total
	None	Small	Large	
Complete resection	24	4	5	33
Incomplete resection	–	1	1	2
Biopsy only or palliative surgery	–	–	3	3

Table 3. Pattern of Relapse

Tumor bulk	Number of patient	Incomplete Tx.		Response		First relapse site		Relapse free
		Give-up	Relapse	CR	PR	Intra-abd.	Extra-abd.	
None	24	2	2 Rt. SCL# Rt. J-D *	20	–	2 Cecum Porta Hepatis	2 Rt. SCL Op. Scar	14
Small	5	1	–	4	–	–	1 Lt. SCL	3
Large	9	1	4 Lt. SCL Lt. SCL Rt. Inguinal Liver	2	2	–	1 Bone	1

Note : # : supraclaviclar lymph node
* : jugulo-digastric lymph node

radiotherapy and 6 cases all died of disease. The relapse rate at 2 years after diagnosis was 25% (6/24) in all cases and was 20% (4/20) in cases with complete treatment. Intra-abdominal relapses were observed only in the cases of primary gastric NHL who were treated by involved field technique with doses over 4,000 cGy. A relapse in porta hepatis made obstructive jaundice and a relapse in the cecum was managed with surgery but progressed to brain metastasis.

In cases with small bulk, all patients responded completely (CR) after treatment and 1 relapse (1/4) was observed at 6 months after treatment.

In cases with large tumor bulk, 44% (4/9) of cases developed systemic dissemination during radiotherapy. And after complete radiotherapy, CR rate was 50% (2/4) and 1 of 2 soon had bone metastasis. So the failure rate was 87.5% (7/8) with exclusion of 1 give-up patient.

The larger the tumor bulk was, the higher the systemic dissemination during radiotherapy, treatment failure, and relapse rate were. And there was no difference in treatment result between cases with no tumor bulk and cases with small tumor bulk.

When chemotherapy was applied to the patients who had systemic progression during radiotherapy or relapsed after completion of radiotherapy using CVP (cyclophosphamide, vincristine, prednisone) or CHOP (cyclophosphamide, Adriamycin, vincristine, prednisone) with or without bleomycin, long-term suvival could be obtained in 33% (2/6). One patient with small tumor bulk relapsed after radiotherapy has been disease free for 31 months and another patient with large tumor bulk who had systemic dissemination during radiotherapy has been disease free for 77 months.

Thus the overall failure rate was 31% in the cases with small or no tumor bulk and was 75% in the cases with large bulk ($p<0.05$).

In calculation of survival, the patients who had incomplete radiotherapy were excluded. Two patients were lost to follow up at 6 and 35 months, and the follow-up rate is 93% (26/28). The follow-up period ranges from 31 to 92 months and its median is 47 months.

The overall suvival at 1, 2, 3, and 5 years were 85.4%, 77.9%, 74.2%, and 68.3%, respectively. And the overall disease free survival (DFS) at 1, 2, 3, and 5 years were 71.4%, 64.3%, 64.3%, and 64.3%, respectively.

The 3 year DFS's were 70% and 75% in patients with no bulk and small bulk. And the 5 year DFS's were same as the 3 year DFS's. And the overall survival rate at 3 and 5 years were 75% and 66% in cases with no bulk, 100% and 100% in cases with small bulk, 45% and 45% in large bulk. In cases with small or no tumor bulk, overall survivals were 79% and 72% at 3 and 5 years, and DFS's were 71% and 71%, respectively. And in cases with large bulk, 3 year DFS was 25% ($p<0.01$). Although the numbers of cases with large bulk were small to be compared with, the survival was related with the tumor bulk before radiotherapy (Fig. 1).

In all patients there was no difference in survival,

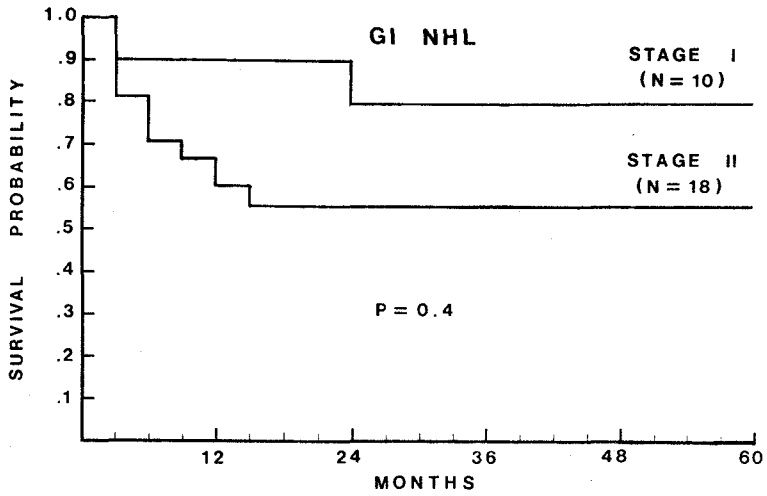

Fig. 1. Disease free survival of 28 cases with primary gastrointestinal NHL after complete radiotherapy by the tumor bulk before radiotherapy.

Table 4. Five Year Overall and Disease Free Survival Rates of 28 Patients with Primary Gastrointestinal NHL after Complete Radiotherapy

	Number of patient	Overall survival	P-value	Disease free survival	P-value
Stage I	10	81.8%		80.0%	
II	18	61.1%	N.S.#	55.6%	N.S.
DPDL	11	72.7%		72.7%	
DH	15	55.8%	N.S.	53.3%	N.S.
Stomach	13	58.6%		61.5%	
Bowel	15	78.8%	N.S.	66.7%	N.S.

Note : #; stastistically not significant

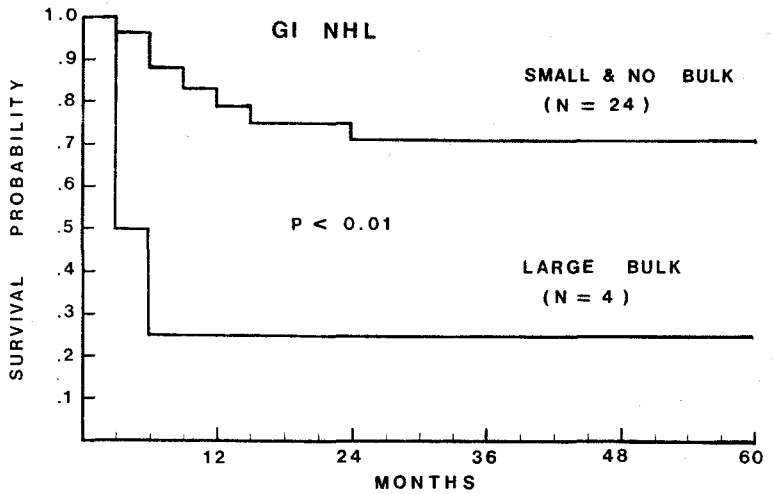

Fig. 2. Disease free survival of 28 cases with primary gastrointestinal NHL after complete radiotherapy by the initial stage.

overall or disease free, by the primary sites and by histologic types. Meanwhile, there was survival difference, overall and disease free, between stage I and stage II without significance (Table 4, Fig. 2). And in cases with no tumor bulk, which consisted the most part of the cases, the aforementioned trends was observed also.

It is noteworthy that 1 patient who gave up radiotherpay at 1,550 cGy without tumor bulk has been disease free for 64 months till now. And in 2 cases with perforation at diagnosis, 1 gave up during treatment and another with large bulk responded partially and was lost with disease.

Patients had the various degree of gastrointestinal upset or bone marrow depression during radiotherapy. But those side reactions were manageable and reversible. Two patients had to rest for a week because of severe degree of leukopenia.

One patient suffered from herpes zoster in her right chest wall at 6 months after radiotherapy. Another patient with no residual in the primary site of stomach experienced the mechanical ileus followed by jejunal perforation at 11 months after radiotherapy. A thick band was found to be the cause of obstruction at 70 cm distal to the previous anastomosis site, and the histologic finding was chronic inflammation with granulation tissue. So the perforation did not seem to be related with previous irradiation.

Thus the radiotherapy technique used in this study was well tolerated by the patients and did not produce severe morbidities.

DISCUSSION

Many factors were identified to affect prognosis. Stage of disease was considered as one of them[1,12,13]. The Ann Arbor system was said to have a degree of success in applying to the nodal NHL, but some reported that certain modification would be necessary[14].

Rudders suggested that division by diaphragm between localized and advanced stage is questionable, with reporting that some patients with extranodal NHL relapsed in solitary extranodal skip sites which might be curable with local treatment. By applying Musshoff's modification, Weingrad reported that stage II_1 (involvement of contiguous regional lymph nodes) had the same survival as stage I[13].

By applying TNM system for gastric adenocarcinoma to the primary gastric NHL, Lim et al showed that poor survival was associated with penetration beyond the serosa or involvement of perigastric lymph nodes[15]. The serosal invasion as the poor prognostic factor was also confirmed in following reports[4,16,17]. The incidence of lymph node involvement was reported 40% to 50%,[3,18~21] but there was no survival over 2 years in cases whose tumor involved beyond regional lymph nodes[3,18].

The diffuse type, especially histiocytic, was reported to be found more often than nodular type in GI NHL[13,15,19,22]. Some reports did not show the survival difference between histologic types[4,13,17,18,23]. While others reported that the nodular types had better prognosis than the diffuse types had[14,15,24].

The gastric NHL was reported to have better survival than the bowel NHL probably due to early diagnosis, tendency for single lesion, and easy treatment with radiation[1].

In general, the patterns of relapse or treatment failure differed between reports because of heterogeneity of the patients studied. When the complete resection was combined with postoperative radiotherapy, the relapse rate was 8% to 25% and the nearly all relapses occurred within 2 years after diagnosis. And the local relapse took zero to 50% among the total relapse[13,16,23,25].

In our cases there was not a true in-field relapse, instead was a case relapsed at the margin of involved radiation field at 3 months after completion of radiotherapy to the stomach primary NHL without tumor bulk. The proper field size is difficult to ascertain. Shiu et al emphasized the importance of extended field due to abdominal relapse out of radiation field, the same type of relapse as we had —obstructive jaundice by celiac or porta hepatis node involvement, in the treatment of the primary gastric NHL with involved field[8]. And it was recommended that target volume should include the gastric bed and high paraaortic lymph nodes for local control of primary gastric NHL in other report[17]. But Reddy suggested that extending the radiation field to include the next echelon of lymph nodes will not improve the treatment result because almost all sites of failure were outside of extended field[26].

Another relapse at the cecum was observed at 22 months after treatment in one case of primary gastric NHL with no tumor bulk in this analysis. There are 2 possible explanation for this relapse;

one is true relapse out of involved field and another is that unnoticed coexistent cecal NHL at the time of diagnosis progressed continuously because we did not check small bowel series before radiotherapy. Both are possible. In 3% to 21 % of GI NHL, multifocal lesions or multiple involvement of more than one segment of bowel were observed[7,21,25,27,28]. Multiple lesions were repoted to have the same prognosis as single lesion has, if the lesions were totally resected[25].

The necessary dose for local control of GI NHL varied between reports. Bush and Ash pointed out that dose of 4,000 to 4,500 cGy in 20 to 25 fractions are needed to achieve a 75% local control[6], and Reddy et al suggested that local recurrence could be reduced with dose higher than 3,000 cGy[26]. Shimm et al suggested a shallow dose response effect for the local control of gastric NHL, from 80% of local control with doses of 2,000 cGy to 90% or more with doses over 4,000 cGy[17]. Diffuse types of NHL were reported to have a slightly higher dose requirement than nodular types have[29~31].

Recently, the prognosis was reported in association with the preradiotherapy tumor bulk rather than the initial stage. In stage I and II primary GI NHL, 10 year survival was 82% in small bulk cases while 12.5% in large bulk cases[25]. And the 5 year survival rate in many report were 40 to 95% in the cases with small tumor bulk and zero to 33% in the cases with large tumor bulk[4,7,15,16,23,32]. And it is said that the patients with positive resection margin were reported to have the same relapse free survival as the patients with clear resection margin[13].

But there was a report that the tumor bulk was also related to stage in the cases with large bulk. The survival of stage I large bulk was 11/14 and tha tof stage II large bulk was 5/23[23].

The result of this analysis also confirm the definite correlation between the tumor bulk and the survival. But the survival of the cases with large bulk was very poor after radiothereapy alone. Many studies recommended chemotherapy when there were risk factors implicationg early dissemination such as non-contiguous lymph node involvement, penetration through serosa, or diffuse histiocytic type[8,16,17,33].

Recently reported results were promising in the treatment of large bulk disease by combined chemotherapy. In large bulk cases when CHOP-Bleo was combined with radiation, relapse decreased from 79% to zero. And even it is recommended that resection should be reserved only for the patients whose tumors were not diagnosable by gastroscopic biopsy or who failed to respond to initial combined radiotherapy and CHOP-Bleo chemotherapy[23]. And another report conservatively recommended combined radiotherapy and chemotherapy when there is doubt about absence of residual tumor, such as liver biopsy or intraabdominal lymph nodes are not obtained[16].

And in extranodal NHL cases of which primary sites and composition of tumor bulk before radiotherapy or chemotherapy were not spectified, combined chemotherapy to radiotherapy reduced the recurrence rate of 50-67% zero to 27% without increasing overall survival rate[34~36].

In conclusion, we confirmed that the prognosis of stage I or II primary gastrointestinal non-Hodgkin's lymphoma was closely associated with the preradiotherapy tumor bulk after operative procedure. And the initial stage was weakly correlated with the treatment results.

In order to increase the local control rate of the cases with small bulk or no residual, especially in the primary gastic NHL, it is recommended to fully encompass the regional nodes in the radiation fields.

And for the survival of the cases of large bulk with dismal prognosis, we think that combined radiotherapy and chemotherapy should be tried.

Most of all for these, it is important to do exact evaluation of tumor extent before radiotherapy or combined treatment.

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= 국문초록 =

I, II기 원발성 위장관 임파종의 수술후 방사선 치료

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일반외과학 교실

최 국 진 · 김 진 복

I, II기 원방성 위장관 임파종 환자 38명의 수술후 방사선 치료 결과를 분석하였다.

방사선 치료중 6예의 원격전이가 관찰되었고, 방사선 치료전 병소의 크기에 따른 치료실패율은 5cm 미만에서 31%, 5cm 이상에서 75%로 유의한 차이가 있었다($p<0.05$).

방사선 치료를 계획대로 받은 28예서 5년 생존율은 69.2%였고, 그중 병소의 크기가 5cm 미만인 경우는 72%였다. 병소의 크기에 따른 5년 무병생존율에도 차이가 있어 5cm 미만인 경우엔 71%, 5cm 이상인 경우엔 25%였다($p<0.05$). 반면에 병기, 병리학적 유형 및 원발장기 등에 따른 생존율의 차이는 유의하지 않았다.

따라서 방사선 치료전 병소 크기가 5cm 미만일 경우는 완치가 가능하나, 5cm 이상으로 클 경우에는 항암화학요법의 병용이 시도될 수 있겠다.