THE SURGICAL TREATMENT OF MALIGNANT LYMPHOMA

MAJOR EDWARD A. GALL, M.C., A.U.S.
POST MEDICAL DIVISION
CAMP MCCOY, WISCONSIN

FROM THE DEPARTMENT OF PATHOLOGY AND BACTERIOLOGY, MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASS.

IT HAS BECOME INCREASINGLY EVIDENT that the gloomy outlook held for individuals suffering from malignant lymphoma must be modified in certain instances.[1] In an earlier study[1, 2] it was shown that attention to cytologic detail permitted a division of these cases into subgroups on the basis of which a considerable range of prognosis could be given. Within each of these subgroups a majority of the patients followed a predictable course. A certain number, however, outlived their fellows to a remarkable degree; in fact some appeared to have been freed of their disease. Among these were many who instead of receiving the usual roentgenotherapy had at the outset been subjected to radical operative procedures.

The present study is concerned with forty-eight such cases which have in common the fact that all grossly perceptible evidence of lymphoma was surgically eradicated at an early operation.

In accordance with the nomenclature utilized in previous studies,[1, 2] these cases have been classified into the following seven groups: Stem cell lymphoma; clasmatocytic lymphoma; lymphoblastic lymphoma; lymphocytic lymphoma; Hodgkin's lymphoma; Hodgkin's sarcoma; and follicular lymphoma. For the details of this classification the reader is referred to the articles cited above. For purposes of comparison with other systems of nomenclature it may be said that the stem cell and clasmatocytic groups probably together comprise the bulk of the tumors commonly included under the term reticulum cell sarcoma.[3, 4] The lymphoblastic and lymphocytic types correspond to what has usually been called lymphosarcoma.[5, 6] Follicular lymphoma has been named giant follicle lymphoblastoma[7] and even giant lymph follicle hyperplasia.[8] The expression cellular Hodgkin's disease is roughly equivalent to our Hodgkin's sarcoma and many authors undoubtedly include these cases as variants of reticulum cell sarcoma.[3, 9]

That great differences in prognosis are associated with variations in cytologic type, may be seen by a glance at Table I (reproduced from the earlier study[1]).

The cases in the present series include, as may be seen in Table II, representatives of each of the subgroups with a predominance (27 out of 48) of the four malignant types. In spite of this apparently unfavorable distribution the median survival period for the group as a whole was 4.5 years, more than twice that of the large control series the majority of the cases of which were treated by roentgenotherapy alone.

The number of cases in certain of the subgroups is undoubtedly too small

TABLE I

DURATION OF MALIGNANT LYMPHOMA (YEARS)

(618 Cases Miscellaneously Treated)[1]

Type	Average	Median
Lymphoblastic lymphoma	1.4	0.6
Hodgkin's sarcoma	1.8	0.9
Stem cell lymphoma	1.7	1.1
Clasmatocytic lymphoma	2.1	1.1
Lymphocytic lymphoma	3.3	2.4
Hodgkin's lymphoma	4.2	3.2
Follicular lymphoma	5.6	5.0

TABLE II

EFFECT ON SURVIVAL

(Radical Surgery versus Roentgenotherapy)

Type	Number of Cases	Range of Survival (years)	Median of Surgical Group (years)	Median of X-Ray Group (years)
Lymphoblastic lymphoma	5	0.2–2.5	0.2	0.6
Hodgkin's sarcoma	2	0.0–0.2	0.2	0.9
Stem cell lymphoma	9	0.0–15.3	5.0	1.1
Clasmatocytic lymphoma	11	0.2–16.5	4.9	1.1
Lymphocytic lymphoma	9	0.0–10.0	5.5	2.4
Hodgkin's lymphoma	9	0.0–19.0	5.4	3.2
Follicular lymphoma	3	4.5–8.5	7.5	5.0

to warrant conclusions. In the stem cell and clasmatocytic groups (20 cases), however, the median survival periods are nearly five times as long as in the control series and in the lymphocytic and Hodgkin's lymphomas (18 cases) nearly twice as long. The figures are sufficiently arresting to justify attention and analysis.

Admittedly, these cases must be considered highly selected from a surgical viewpoint, since there have been excluded those in which the operator was not satisfied that he had removed all visible and palpable neoplastic tissue. It is believed, however, that the cases chosen may be considered as fairly representative of the lymphomatous group of diseases. All seven types were present. The age and sex incidences of the surgical series are identical with those of the larger series previously reported. The average age at onset was 41.1 years, and the proportion of males to females was 2:1.

There was wide variation in the duration of symptoms preceding operation, ranging from a few days (recorded as 0.1 years) to five years. The average preoperative duration of symptoms was 1.0 years, the mean 0.5 years. In the larger series of miscellaneously treated cases the average pretreatment period was 1.3 years. It does not appear, therefore, that the patients included in the present study received therapeutic attention significantly earlier than the general run of individuals with the same disease. Moreover, it is apparent from Table III that the preoperative duration of symptoms bore no relationship to postoperative survival.

None of the patients received preoperative roentgenotherapy, which is not surprising since the histologic nature of the lesion was unsuspected in

TABLE III

CASES TREATED WITH RADICAL SURGERY

Case	Type	Location	Preop. Duration (Years)	Postop. Duration (Years)	Postop. Recurrence (Years)	Postop. Radiation	Status
1	Lymphoblastic	Cecum	0.5	0.2	?	Prophylactic	Dead
2	Lymphoblastic	Jejunum	1.0	1.5	0.8	Prophylactic	Dead
3	Lymphoblastic	Rectum	0.1	0.2	0	Prophylactic	Dead
4	Lymphoblastic	Stomach	3.0	0.2	0.2	0	Dead
5	Lymphoblastic	Sigmoid	1.0	2.5	1.0	Recurrence	Dead
6	Hodgkin's sarc.	Jejunum	0.5	...	...	0	Lost
7	Hodgkin's sarc.	Ax. L. N.	3.5	0.2	0.2	Recurrence	Dead
8	Stem cell	Cerv. L.N.	0.5	11.5	1.5	Recurrence	Dead
9	Stem cell	Thigh	0.7	15.3	7.0	Prophylactic	Dead
10	Stem cell	Cord (epidural)	0.1	2.6	2.0	Prophylactic	Lost
11	Stem cell	Skin (arm)	0.5	10.0	0	Prophylactic	Alive
12	Stem cell	Stomach	3.5	0	0	0	Dead
13	Stem cell	Cerv. L.N.	0.5	9.0	0.2	Recurrence	Alive
14	Stem cell	Stomach	1.5	5.0	5.0	0	Dead
15	Stem cell	Cecum	1.0	0.3	0.3	Prophylactic	Dead
16	Stem cell	Stomach	0.2	0.5	0.2	Recurrence	Dead
17	Clasmatocytic	Appendix	0.1	0.2	0.2	Recurrence	Dead
18	Clasmatocytic	Stomach	0.1	0.2	0	0	Dead
19	Clasmatocytic	Jejunum	0.1	0.2	?	Prophylactic	Dead
20	Clasmatocytic	Humerus	0.9	16.5	7.0	Recurrence	Alive
21	Clasmatocytic	Stomach	0.8	6.2	0	Prophylactic	Alive
22	Clasmatocytic	Stomach	0.6	4.4	3.0	0	Dead
23	Clasmatocytic	Tibia	2.0	7.0	0	0	Alive
24	Clasmatocytic	Femur	0.2	6.1	0	0	Alive
25	Clasmatocytic	Stomach	1.0	6.0	0	0	Alive
26	Clasmatocytic	Cerv. L.N.	0.5	5.0	5.0	Prophylactic	Alive
27	Clasmatocytic	Maxill. antrum	0.1	3.0	0	Prophylactic	Alive
28	Lymphocytic	Cerv. L.N.	0.3	1.6	0.1	0	Dead
29	Lymphocytic	Ileum	0.2	...	?	0	Lost
30	Lymphocytic	Eyelid	?	8.0	0	0	Lost
31	Lymphocytic	Cerv. L.N.	0.3	3.5	3.5	Recurrence	Lost
32	Lymphocytic	Stomach	0.1	7.0	0	Prophylactic	Alive
33	Lymphocytic	Skin – back	0.1	10.0	0	0	Alive
34	Lymphocytic	Femur	2.0	8.0	2.0	0	Alive
35	Lymphocytic	Parotid	5.0	6.0	3.0	Prophylactic	Alive
36	Lymphocytic	Parotid	0.2	3.5	0	Prophylactic	Alive
37	Hodgkin's	Ing. L.N.	0.1	19.0	0	Prophylactic	Alive
38	Hodgkin's	Cerv. L.N.	0.1	5.4	?	Prophylactic	Dead
39	Hodgkin's	Submaxill.	2.0	3.0	0	0	Dead
40	Hodgkin's	Cerv. L.N.	4.0	15.0	0.2	Recurrence	Alive
41	Hodgkin's	Colon	0.6	0	0	0	Dead
42	Hodgkin's	Ax. L.N.	1.0	5.5	0	Prophylactic	Alive (Tbc)
43	Hodgkin's	Cerv. L.N.	0.9	0.6	0.3	Prophylactic	Dead
44	Hodgkin's	Cerv. L.N.	4.0	10.0	6.0	Recurrence	Dead
45	Hodgkin's	Cerv. L.N.	0.8	2.0	2.0	Prophylactic	Lost
46	Follicular	Ing. L.N.	2.0	4.5	0	0	Dead
47	Follicular	Ing. L.N.	0.5	8.5	0	Prophylactic	Alive
48	Follicular	Cerv. L.N.	1.0	7.5	0	Prophylactic	Alive

almost all instances. Had the character of the process been known, it is probable that the dictates of custom would have precluded operation in the majority of the cases herein reported. Postoperative prophylactic irradiation was administered to 21 patients in amounts varying from 600 r. to 1800 r. The results were inconclusive, and it is not possible to comment concerning the efficacy of the procedure. Thirteen other patients received irradiation at a later time for recurrence of the original tumor. The response in these individuals was satisfactory in eight instances.

Six of the 48 patients were considered lost, although three remained under observation after operation for 2.6 years, 3.5 years and 8 years, respectively. Twenty-three cases were known to be dead but among these were several dead of causes unrelated to lymphoma. Nineteen patients were alive, and only one of these had shown evidence of lymph node disease at the last examination. All of the others had been free of symptoms or objective signs for three or more years.

Recurrence, either locally or elsewhere, was observed in 23 patients. The recurrence had appeared an average of 2.2 years after operation although in eight patients there had been an interval of three to seven years. Among the 23 patients who died there were 13 with recognizable lymphomatous lesions at the time of death, four in whom the cause of death was unknown and six with no evidence of lymphoma. The latter included five cases dying shortly after operation the deaths being presumably surgical in nature. Obviously, insufficient time had elapsed in these to permit the development of recurrence.

Six of the dead cases were necropsied. In four (0.2, 0.25, 2.5 and 10 years after operation) extensive lymphomatous infiltration was found. One case dead of postoperative intestinal obstruction and another who died of prostatism and peritonitis 4.5 years after operation showed no persistent residua of neoplastic disease.

Exclusive of the two cases who disappeared immediately after discharge from the hospital, the average postoperative survival period for all cases was 5.2 years and the overall total duration from the date of onset was 6.9 years. These figures are, respectively, two times and almost three times the levels of similar figures obtained from identical cases treated by other means.

TABLE IV

"CURED" CASES OF MALIGNANT LYMPHOMA

Case	Type	Location	No Evidence Disease (Years)	Total Duration (Years)	Status
11	Stem cell	Skin—arm	10.0	10.5	Alive
13	Stem cell	Cerv. L. N.	9.0	9.5	Alive
20	Clasmatocytic	Humerus	9.5	17.4	Alive
21	Clasmatocytic	Stomach	6.2	7.0	Alive
23	Clasmatocytic	Tibia	7.0	9.0	Alive
24	Clasmatocytic	Femur	6.1	6.3	Alive
25	Clasmatocytic	Stomach	6.0	7.0	Alive
27	Clasmatocytic	Max. antrum	3.1	3.1	Alive
30	Lymphocytic	Eyelid	8.0	8.0	Lost
32	Lymphocytic	Stomach	7.0	7.1	Alive
33	Lymphocytic	Skin—back	10.0	10.1	Alive
34	Lymphocytic	Femur	6.0	10.0	Alive
35	Lymphocytic	Parotid	3.0	11.0	Alive
36	Lymphocytic	Parotid	3.5	3.7	Alive
37	Hodgkin's	Ing. L. N.	19.0	19.1	Alive
40	Hodgkin's	Cerv. L. N.	14.8	19.0	Alive
42	Hodgkin's	Axill. L. N.	5.5	6.5	Alive (Tbc)
46	Follicular	Ing. L. N.	4.5	6.5	Dead
47	Follicular	Ing. L. N.	8.5	9.0	Alive
48	Follicular	Cerv. L. N.	7.5	8.5	Alive

Listed in Table IV are 20 cases, 18 of them still alive, one dead without evidence of lymphoma at necropsy 4.5 years after the excision of the primary process, and one patient lost from observation eight years after operation. Five of the patients had had local recurrence. These were treated by secondary excision in two and irradiation in three. They had had no further evidence of their disease 3.0, 6.0, 8.8, 9.5, and 14.8 years since the secondary procedure. Another case, although apparently free from lymphoma for five years, has been institutionalized for active pulmonary tuberculosis. The average postoperative survival for this group of 20 cases is eight years, and both the average and mean total duration nine years. They have, thus, as a group exceeded all expectations for survival, and those living are clinically apparently free of lymphoma.

Discussion.—It seems obvious that a blanket prohibition of surgical therapy in malignant lymphoma is unwarranted. It is equally apparent, however, that relatively few cases are susceptible to this therapeutic method. Comparatively few patients have sufficiently localized and accessible lesions when first encountered. It is of interest that among 135 necropsies upon lymphomatous individuals the lesions were completely localized in 10 per cent of the subjects.[1] This figure cannot be considered representative of the proportion of tumors which might be treated surgically since a significant number appear in inaccessible regions and not a few may remain sufficiently obscure clinically so that the need for exploration may fail to materialize. In the event that the lesion is circumscribed, reasonably limited in size and accessible technically there seems to be no factual basis for the avoidance of surgery.

The question of diagnostic biopsy as a preliminary to radical operation raises a moot point. A discussion as to whether or not the procedure may be a means of dissemination does not lie within the province of this paper. The need for biopsy arises in so many instances that it will be practiced whatever the individual opinion. Under such circumstances, however, the following observation is distinctly worthy of recognition. In a group of 33 cases with malignant lymphoma of the gastro-enteric tract only four showed metastasis to regional lymph nodes. In 16 instances lymph nodes had seemed to be the seat of metastasis at gross examination but showed only banal inflammation or hyperplasia upon microscopic examination. It is recommended, therefore, that if biopsy is contemplated it should be made within the primary visceral lesion, when there is one, and not in adjacent lymph nodes even if they appear to be involved to inspection or palpation. On many occasions diagnostic biopsy has been unsuccessful when this recommendation has been ignored. It is surprising but nonetheless true that a disease so prone to rapid dissemination through the lymph node system should upon affecting a viscus primarily be less likely to spread in this manner than carcinoma in the same location.

Reference to the survival figures can permit no doubt that surgical

eradication does improve the prognostic outlook in selected cases of lymphoma.[10, 11, 12] This is most strikingly the case in the reticulum cell sarcoma group (stem cell and clasmatocytic lymphoma). Is it possible that the surgical success is apparent only and can be attributed to other factors? Since all types of malignant lymphoma comprised this series it would appear that there was no selection on a histologic basis. As a matter of fact the majority of patients in this series suffered from the more malignant forms of lymphoma. It is within the realm of possibility that the extranodal location of these lesions may have caused modification in the clinical course. Prolonged survival of this sort has been recorded elsewhere, notably with lesions of bone and skin. This is belied in part by the presence of 16 primary nodal cases in the present series and further emphasized by the fact that seven of these appeared in the so-called "cured" group (Table IV). Moreover, in an analysis of our own material there were found 31 cases with primary lymphomatous involvement of a viscus or bone which at the time of initial examination appeared to be circumscribed. In contradistinction to the present group these cases were treated after biopsy by irradiation alone. Although the range of survival in these extended from 0.1 to 9.3 years the average total duration was 2.1 years and the median 1.0 years. The distribution and histologic nature of the lesions were similar to those in the group of surgically treated cases. It would seem, then, that neither the location of a lesion nor its morphologic structure could account for the improvement of prognosis observed following radical surgery.

The question of the advisability of postoperative prophylactic irradiation to the operative site cannot be answered with certainty. Twenty-one cases were so treated, and among these eight suffered recurrence, ten had no recurrence, and in three the outcome is not known. It is probably wiser to administer irradiation to those cases in which the surgeon does not feel confident that he has extirpated all foci of involvement. Preoperative irradiation would seem to be pointless except in those cases in which a bulky tumor might be made more available to surgical manipulation as the result of shrinkage caused by roentgen radiation. Under other circumstances it should be appreciated that irradiation can so affect a lesion as to render its histologic identification impossible or so disturb adjacent tissues as to interfere with both the surgical procedure and subsequent healing.

In a disease as prone to clinical variation and in which progression may occur insidiously without overt manifestation it would be foolhardy indeed to claim that cures are effected by any means. It seems reasonable to state, however, that cases judiciously selected in the manner indicated above may, if treated by radical surgery, experience far better results than might be anticipated from roentgenotherapy alone.

SUMMARY AND CONCLUSIONS

1. This study concerns itself with 48 cases of malignant lymphoma of all types, with sufficient localization to permit radical surgical excision.

2. Despite several deaths immediately after operation the average postoperative duration was 5.2 years and the average total duration 6.9 years.

3. These figures were significantly greater than those obtained from other cases treated by irradiation alone.

4. There were 20 cases without residual evidence of lymphoma including one which came to necropsy 4.5 years after operation. The average total duration of these cases was nine years and the postoperative range extended from 3 to 19 years.

5. It is believed that radical surgery has a very definite place in the treatment of certain cases of malignant lymphoma and that apparent freedom from the disease for long periods of time has resulted in many individuals so treated.

REFERENCES

[1] Gall, Edward A., and Mallory, Tracy B.: Malignant Lymphoma. A Clinical Pathological Survey of 618 Cases. Amer. Jour. Path., **18**, 362, 1942.

[2] Gall, E. A., Morrison, H. R., and Scott, A. T.: The Follicular Type of Malignant Lymphoma: A Survey of 63 Cases. Ann. Int. Med., **14**, 2073, 1941.

[3] Roulet, F.: Weitere Beitrage Zur Kentniss des Retothelsarkoms der Lymphknoten und Anderen Lymphoiden-Organe. Virch. Arch., **286**, 702, 1932.

[4] Parker, F., Jr., and Jackson, H., Jr.: Primary Reticulum Cell Sarcoma of Bone. Surg., Gynec. & Obst., **68**, 45, 1939.

[5] Ewing, J.: Neoplastic Diseases. 3rd Edit., W. B. Saunders, Co., Phila., 1928.

[6] Ehrlich, J. C., and Gerber, I. E.: The Histogenesis of Lymphosarcomatosis. Amer. Jour. Ca., **24**, 1, 1936.

[7] Baehr, G.: The Clinical and Pathological Picture of Follicular Lymphoblastoma. Trans. Assn. Amer. Phys., **47**, 330, 1932.

[8] Brill, N. E., Baehr, G., and Rosenthal, N.: Generalized Giant Lymph Follicle Hyperplasia of the Lymph Nodes and Spleen. J. A. M. A., **84**, 669, 1925.

[9] Callender, G. R.: Tumors and Tumor Like Conditions of the Lymphocyte, the Myelocyte, the Erythrocyte and the Reticulum Cell. Amer. Jour. Path., **10**, 443, 1934.

[10] Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma: A Study of 196 Cases with Biopsy. J. A. M. A., **115**, 17 and 112, 1940.

[11] Craver, L. F.: Five-Year Survivals in Lymphatic Tumors. Surg., Gynec. & Obst., **60**, 485, 1935.

[12] Stout, A. P.: Is Lymphosarcoma Curable? J. A. M. A., **118**, 968, 1942.