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Surgical Reduction of Tumour Bulk in Management of Abdominal Burkitt's Lymphoma

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Summary

The results of a retrospective study of the value of reductive surgery in the treatment of abdominal Burkitt's lymphoma are reported. Nine patients had almost complete removal of the tumour, 16 had little over half of the tumour removed, and 43 underwent biopsy only. All patients subsequently received chemotherapy. There was a highly significant difference in the proportion of patients achieving a sustained durable remission ($P > 0.0001$) and a significant difference in survival ($P > 0.05$) between the group having almost complete removal and the partial resection group. Partial resection gave no advantage over no surgery. We believe that whenever possible complete removal of the abdominal tumour should be attempted regardless of the presence of extra-abdominal tumour; but unless at least 90% of the tumour can be removed there is no advantage in partial resection in terms of response to subsequent chemotherapy. In particular the removal of one of two involved ovaries can no longer be recommended. The implications of these results are related to cancer treatment strategy.

Introduction

Burkitt's lymphoma is an exceptional tumour in many respects, not least of which is its dramatic response to chemotherapy. Some 80% of all patients admitted to the Lymphoma Treatment Centre, Kampala, achieve complete clinical remission after chemotherapy (Ziegler, 1972), and though about two-thirds of these relapse the overall predicted long-term survival rate based on 185 patients treated at the centre between 1967 and 1972 is 57% (Magrath and Ziegler, 1973). The relapse and survival rates depend largely on whether abdominal tumour is present. Where there is only extra-abdominal tumour, regardless of site, cumulative long-term

survival is 82%, whereas with abdominal tumour (not extensively resected surgically) it ranges from 29% to 52% depending on the presence and site of extra-abdominal tumour (table I). This finding raises the question whether complete or nearly complete resection of abdominal tumour, when possible, would improve the response to chemotherapy in terms of relapse and survival. Since 39% of male patients and 73% of female patients with Burkitt's lymphoma have abdominal involvement, and since ovarian tumour, which is readily resected, accounts for over half of the abdominal tumours in female patients (Magrath, 1974 a), this is an important consideration.

TABLE I—Clinical Staging of Burkitt's Lymphoma and Relation to Prognosis. Results were Calculated Actuarially (see Text)

	Extent of Tumour	Survival Rate (100 Weeks or More)	Remission Rate* (50 Weeks or More)
Stage A	Single tumour outside abdomen	82%	61%
Stage B	Multiple extra- abdominal tumours (includ- ing nervous system)	82%	24%
Stage C	Abdominal tumour with or without facial tumour	52%	16%
Stage D	Abdominal tumour with tumour at other sites (except face alone)	29%	10%

*Remission rate represents proportion of patients who have not relapsed.

Previously chemotherapy has been used as an adjunct to surgery, putatively to prevent the development of metastases (Nora and Preston, 1963; Fisher, 1972). This mode of utilization, however, has met with little success (Wolff *et al.*, 1968; Fisher, 1972), and in multicentric tumours or tumours which are potentially widely disseminated from the outset—for example, the lymphomas—a radically different approach has been necessary. In these cases there has been a reversal of roles, with surgery in effect being used as a relatively minor adjunct to chemotherapy. In the treatment of abdominal Burkitt's lymphoma surgery has possibly a much more important place, and in this paper we attempt to evaluate the potential advantages of a combined surgical and chemotherapeutic approach and in particular to determine the importance of the extent of surgical resection of tumour bulk. Since radiotherapy is unavailable in Uganda it played no part in the treatment of these patients.

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Patients and Methods

All patients admitted to the Lymphoma Treatment Centre during August 1967 to August 1972 with cytologically or histologically proved Burkitt's lymphoma and treated by chemotherapy were subjected to analysis. Only surgery of the initial tumour was considered, and its effectiveness is therefore probably best judged on the unmaintained sustained remission rate—that is, the proportion of patients who achieve complete remission and never relapse. Prolonged, tumour-free survival (in effect, cure) is, of course, the ultimate aim of therapy, and we therefore also assessed the value of surgery in terms of survival rate, a measurement which, however, is dependent also on the efficacy of relapse treatment.

Comparison of groups of patients subjected to extensive or partial resection or not operated on was based on actuarial prediction of complete remission and survival rates at 50 and 100 weeks respectively (referred to here simply as remission and survival rates), for at these points the actuarial curves become horizontal and relapse or tumour-related death thereafter is very unlikely (Ziegler *et al.*, 1972 a). The χ^2 test was used to assess the statistical significance of differences between the groups, taking account of the sum of the individual follow-up periods of the patients in each group.

Extent of Surgical Resection.—Patients with intra-abdominal tumours presented at a variety of hospitals in Uganda. In most cases they were referred at once to the Lymphoma Treatment Centre. Some, however, underwent laparotomy at the referring hospital before being transferred. At the centre all patients who were fit enough were subjected to laparotomy, and whenever possible extensive surgical reduction of tumour bulk was attempted, since it has been suggested that this is of value (Morrow *et al.*, 1967). Whether this was achieved, however, depended in part on the organs involved. Mesenteric, bowel, and splenic masses were usually amenable to total resection. On the other hand, when both kidneys or a large part of the liver were involved or the tumour was arising from retroperitoneal tissues only partial resection could be achieved. In the case of bilateral ovarian involvement the policy at the centre was to remove only one ovary, thus, hopefully, to achieve reduction in tumour bulk without sterilizing the patient and necessitating replacement hormonal therapy. At up-country hospitals, however, bilateral ovarian tumour was removed completely. These patients, therefore, are worthy of particular consideration; since the operative procedure depended on whether surgery was performed in the referring hospital or at the centre it was in effect decided at random. In addition the sites and extent of the tumours were closely comparable whether one or both ovaries were removed. Patients who were not operated on were in general unfit for surgery, usually because of more extensive tumour. This group therefore had potentially a worse prognosis than the others.

Allocation to Groups.—Altogether 190 patients with Burkitt's lymphoma were admitted to the Lymphoma Treatment Centre during the five-year period. Of these, 91 (48%) had tumour involving intra-abdominal organs and 41 were subjected to laparotomy (table II). Details of tumour sites, operative procedure, chemotherapy, and relapse and survival were extracted from the records and the patients were divided into three groups according to the extent (if any) of surgical reduction. Those who had had at least 50% but less than 90% of the tumour removed—for example, the largest of two involved ovaries—were allocated to the "partial resection" group (16 cases); in most of these patients little more than half of the tumour was excised. Patients who had had almost all of the tumour removed—both affected ovaries, for example (performed only at the referring hospital), or a mesenteric mass—were designated "extensive resection group" (9 cases); these patients had had at least 90% of their tumour removed, and often all the visible tumour (prob-

ably 99% or more). Where only biopsy was performed at laparotomy (3 cases) or laparotomy was not performed (40 cases) the patient was allocated to the "non-surgical group" (43 cases). In five cases there was no indication of the amount of tumour removed at operation, and these were excluded from the analysis. A further 14 patients were excluded from the calculations of remission rate and survival because they had died within two weeks of presentation (11 would have been in the non-surgical group and 3 in the partial resection group), and three others were excluded because they could not be followed up (two with extensive resection and one with partial resection).

TABLE II—Data on Patients who had Laparotomy

	No. of Patients
Over 90% of tumour removed	9
Removal of 50-90% of tumour	16
Biopsy only	3
Unknown quantity of tumour removed	5
Operative deaths (within 2 days)	4*
Early deaths (2-14 days)	1†
Sent back to referring hospital	2
Insufficient follow-up	1
Total	41

*Three of these patients had partial tumour resection (one of whom died before recovery from the anaesthetic) and one had biopsy only. A further patient, not included here, died during the induction of anaesthesia.

†This patient had biopsy only.

Chemotherapy.—On the day of surgery or as soon as the diagnosis had been made all patients were given a single dose of cyclophosphamide (40 mg/kg intravenously) then entered into a controlled therapeutic trial designed to compare the efficacy of this alone with that of six doses of cyclophosphamide (Ziegler *et al.*, 1970) or the latter with that of a combination of drugs known as TRIKE (Ziegler *et al.*, 1972 b). Remission and survival rates were similar whichever form of therapy was used (Ziegler, 1972). Patients with meningeal tumour infiltration were treated with intrathecally administered drugs (Ziegler and Bluming, 1971).

Results

Actuarially predicted remission and survival rates (figs. 1 and 2) showed a clear advantage in patients who had undergone extensive surgical reduction of tumour (56% and 89% respectively) compared with those who had had only partial

FIG. 1—Actuarial curves of complete remission rates—that is, patients who are completely free from tumour and have not relapsed. After initial chemotherapy no further treatment was given unless patient relapsed. Points on lower two curves before 15 weeks represent several patients (up to 11), but thereafter and on upper curve each point corresponds to single patient. Some of these patients had one or more relapses and appear on pre-plateau part of curves. Others never relapsed.

TABLE III—Statistical Comparison of the Three Groups of Patients

Group	No. of Patients	Survival Rate	No. of Deaths		Total Patient-Weeks of Survival*	χ^2	P	Remission Rate	No. of Relapses†		Total Patient-Weeks of Remission‡	χ^2	P
			Observed	Expected					Observed	Expected			
Extensive	9	89%	1	4.7	1,564	4.5	<0.05	56%	4	12.4	1,142	16.3	<0.0001
Partial	16	45%	8	4.3	1,438			11%	14	5.6	513		
None	43	37%	8	10.1	1,438	0.36	>0.5†	11%	14	13.2	513	0.007	>0.95†
Extensive	9	89%	26	23.9	3,400			14%	37	37.8	1,464		
None	43	37%	1	7.5	1,564	8.4	<0.005	56%	4	18.0	1,142	17.9	<0.0001
			26	18.5	3,400			14%	37	23.0	1,464		

*Sum of individual follow-up periods—either until death or until date last seen alive.

†Not significant.

‡This includes patients who never achieved complete remission and those who relapsed after period of complete remission.

§Sum of individual periods of complete remission dated from start of treatment.

FIG. 2—Actuarial curves of survival of patients having extensive, partial, or no surgery. Each patient is shown individually in upper two curves but in non-surgical group, which was larger, some points in descending part of curve (before 50 weeks) represent up to three patients.

resection (11% and 45% respectively). Whereas prognosis after extensive surgery approximated to that of stage A patients (see table I), after partial resection remission and survival rates were similar to those in the non-surgical group (14% and 37% respectively). The differences in prolongation of remission and survival between the extensive and partial resection groups were statistically significant ($P < 0.001$ and $P < 0.05$ respectively; table III). These results were unlikely to be altered by further follow-up of the patients since only one living patient in each group remained at significant risk of relapse having been in complete remission for less than one year.

The one patient in the extensive resection group who died had developed multiple cranial nerve palsies and paraplegia shortly after resection of bilateral ovarian tumours. She had a partial response to chemotherapy and died from staphylococcal septicaemia after receiving methotrexate. The outcome had she not died from septicaemia remains in doubt.

The close similarity between the extensive and partial resection groups (table IV) indicates that the difference in

prognosis were due entirely to the surgical procedure. The non-surgical group contained more patients with extensive disease than did the other groups. There was a predominance of females in the surgical groups, and this is related to the high frequency (Magrath, 1974 a) and ease of resection of ovarian tumours. There was, however, no significant difference in remission and survival rates between males and females in the no-surgery group, and the similarity of prognosis between the partial resection (with an excess of females) and no-surgery groups further confirmed that sex was not a factor in the response to chemotherapy. Comparisons of different treatment subgroups in the partial resection and no surgery groups confirmed the lack of influence of the treatment regimen on prognosis (Ziegler, 1972).

TABLE IV—Comparison of Groups

	Extensive Resection	Partial Resection	Non-surgical
No. of patients	9	16	43
Average age (yr)	6	7.5	7.5
Age range (yr)	4-16	4-14	3-60*
Males: females	2:7	2:14	21:22
Clinical stage:			
C	7 (78%)	12 (75%)	20 (46%)
D	2 (22%)	4 (25%)	23 (54%)
Therapy:			
Cyclophosphamide 1 or 2 doses	6 (67%)	7 (44%)	14 (33%)
Cyclophosphamide 6 doses	3 (33%)	3 (19%)	21 (49%)
TRIKE	0	6 (38%)	8 (18%)

*One patient was aged 60 and one was aged 25 years but all the others were aged 15 years or less.

TRIKE = Sequential combination of cyclophosphamide, vincristine, methotrexate, and cytosine arabinoside.

BILATERAL OVARIAN TUMOURS

The overall results did not differ when only females with bilateral ovarian tumours were considered (table V). All 10 patients who had unilateral oophorectomy relapsed, whereas only one in the bilateral oophorectomy group relapsed. Further, none of the living patients in the latter group remained at significant risk of relapse since all had been in remission for over 50 weeks. Survival was significantly longer in the bilateral oophorectomy group than in the unilateral oophorectomy group.

TABLE V—Statistical Comparison of Response to Chemotherapy after Removal of Both, One, or Neither of Bilaterally Affected Ovaries

Surgical Procedure	No. of Patients	Survival Rate	No. of Deaths		Total Patient-Weeks of Survival*	χ^2	P	Remission Rate	No. of Relapses†		Total Patient-Weeks of Remission‡	χ^2	P
			Observed	Expected					Observed	Expected			
Both	6	83%	1	4.8	1,190	5.7	<0.025	83%	1	9.9	1,184	60.6	<0.00001
One	10	18%	7	3.2	785			0%	10	1.1	138		
Neither	10	18%	7	5.0	785	0.89	>0.3†	0%	10	5.8	138	3.7	>0.05†
Both	7	57%	3	5.0	782			15%	6	10.2	245		
Neither	6	83%	1	2.4	1,190	0.52	>0.4†	83%	1	5.8	1,184	18.6	<0.0001
	7	57%	3	1.6	782			15%	6	1.2	245		

*Sum of individual follow-up periods—either until death or until date last seen alive.

†Not significant.

‡Includes patients who never achieved complete remission and those who relapsed after period of complete remission.

§Sum of individual periods of complete remission dated from the start of treatment.

For comparison a group of patients in whom bilateral ovarian tumour was the only clinically detectable intra-abdominal tumour but in whom surgery was not undertaken is included in table V. Survival and remission were not significantly worse than in patients who had unilateral ovarian resection. Any differences, in fact, tended to favour the no-surgery group.

Patients with bilateral ovarian tumour in the no-surgery or partial resection group did not have any prognostic advantages over other patients in these groups.

Discussion

These results show that patients in whom intra-abdominal Burkitt's lymphoma was extensively resected had greatly improved prognosis, so that remission and survival rates after chemotherapy were similar to those of patients in whom abdominal tumour was never present. This was, however, a retrospective study and numbers were small, so that a degree of caution is indicated. Nonetheless, the differences in prognosis induced by extensive surgery, particularly in the proportion of patients that never relapse, are of sufficient magnitude to be most unlikely to be due entirely to chance. Imbalance between the surgical groups with regard to clinical stage, age, sex, and treatment was not present, and in any case the last three factors did not significantly influence prognosis in the non-surgical group. The possibility that the criterion of "fit for laparotomy" itself was of decisive importance is excluded by the closely similar remission and survival rates in the partial resection and no-surgery groups. Finally, the similarity of the overall findings in the 60% of patients in each surgical group who had bilateral ovarian involvement as their sole abdominal tumour, in whom the decision on extent of removal was effectively random, quantitation of resected tumour was very precise (removal of the largest or both ovaries), and potential differences in prognosis related to sex and variation in intra-abdominal tumour sites were excluded, lends strong support to the conclusion that extensive surgery results in a greatly improved prognosis.

It is reasonable to conclude that the response to chemotherapy depends primarily on the tumour volume at the start of drug treatment but that relatively large differences are necessary before significant differences in prognosis are detectable—that is, 90 to 99% or 10- to 100-fold (equivalent to one or two logarithm differences in cell number). This implies in turn that the clinical staging system, which was derived from the remission and survival rates, is basically a reflection of differences in tumour volume and that patients with stage C or D disease may be converted by surgery to stage A or B.

TREATMENT OF CHEMOTHERAPY-SENSITIVE TUMOURS

The benefit of extensive surgery of Burkitt's lymphoma is in line with currently accepted concepts of the kinetics of chemotherapy (Skipper, 1970) and the role of host antitumour mechanisms (Klein, 1969; Ngu *et al.*, 1970). In the case of tumours above a critical volume the amount of chemotherapy required to reduce tumour cell number to a level at which host defence mechanisms can control growth or destroy the residuum is often unacceptable in terms of toxicity and immunosuppression, so that cure is rarely achieved. Extensive surgery followed immediately by chemotherapy (thus preventing tumour regrowth which occurs between doses of drugs) may give rise to a situation in which an acceptable amount of chemotherapy in terms of immunosuppression is sufficient to reduce tumour volume to the level at which the host can cope with remaining cells. An additional advantage

is that tumour-related immunosuppression, which has been described in a variety of animal (Linder, 1962; Matsuyama and Nakamura, 1964) and human tumours (Lamb *et al.*, 1962; Robinson and Hochman, 1966), including Burkitt's lymphoma (Stjernsward *et al.*, 1970; Magrath, 1974 b) is likely to be rapidly relieved, so that host immunological mechanisms are optimally effective.

If the experience with Burkitt's lymphoma is relevant to other tumour systems then the most dramatic improvements in results with large tumours are likely to be gained by emphasizing initial cytoreduction, utilizing all therapeutic modalities to their maximum extent, rather than prolonged intensive chemotherapy programmes which may have little chance of increasing the cure rate in tumours above a critical size.

Tumours in which this approach may be particularly valuable include lymphomas, choriocarcinoma, and some embryonal tumours, which are often highly sensitive to chemotherapy and amenable to extensive resection. Other means of bulk reduction should also be considered. Radiotherapy with its associated immunosuppression (Stjernsward *et al.*, 1972) and often prolonged persistence of tumour antigen may or may not be equivalent to surgery, but cytophoresis by means of a cell centrifuge in leukaemias is worthy of study.

DISADVANTAGES OF SURGERY

In this series the surgical mortality rate was 10%. Clearly, where extensive resection was achieved the risk was confined to that of the surgical procedure itself. The possibility of tumour dissemination when only partial resection is accomplished, however, must be considered, and this could explain the tendency for patients who had unilateral oophorectomy to have shorter remission duration and survival than patients with bilateral ovarian tumours treated by chemotherapy alone, though our figures do not permit a definite conclusion to be made.

A further consideration is the benefit of bilateral oophorectomy versus sterility and the necessity of hormonal replacement therapy. Our findings suggest that the chance of survival is approximately doubled by extensive resection. The disadvantages of castration depend to some extent on the environment. In Uganda tribal folk-lore and the difficulties of continued replacement therapy must be considered, as well as the feelings of the individual (if old enough to understand). Apart from rare, exceptional cases, however, most patients would probably wish to increase their chance of cure by every possible means.

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MEDICAL MEMORANDA

Meningioma Mimicking Features of a Pheochromocytoma

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We report a case of a supratentorial meningioma in a patient who had episodic hypertension responsive to α - and β -blockade and associated with an excess urinary excretion of vanilmandelic acid (VMA). After excision of the tumour VMA excretion became normal.

Case Report

A 55-year-old woman was admitted through the casualty department, having been found lying in a street. She had experienced headache and vomiting and her employer volunteered symptoms suggestive of organic confusion in the patient, but a detailed history was unobtainable.

On examination her weight was 69 kg, and her blood pressure 195/120 mm Hg. She had complete right third nerve palsy and flaccid left hemiparesis. The results of skull and chest x-ray examinations and intravenous pyelography were normal. A lumbar-puncture showed clear fluid and a pressure of 270 mm. E.E.G. showed right-sided abnormality. A right carotid angiogram showed a vascular tumour supplied by the middle cerebral artery in the region of the lesser wing of the right sphenoid bone, and a biopsy specimen of the tumour showed transitional cell meningioma.

During the days taken to complete these investigations her level of consciousness gradually deteriorated, and she did not respond to dexamethasone. After the excision of her meningioma the conscious level lightened for a few days but then relapsed and remained unchanged until her death.

Before the tumour was removed the patient remained hypertensive, and episodic increases of the hypertension to 215/150 mm Hg with tachycardia occurred. On the five occasions when 24-hour urine specimens were assayed for VMA an excess was de-

tected (see table). The blood urea was in the normal range during the whole illness. The blood pressure evanescently responded to 10-mg, but not 5-mg, intravenous doses of phentolamine, and both hypertension and tachycardia responded to β -blockade. After tumour excision the level of VMA excretion became normal, but the hypertension persisted.

The patient died of bronchopneumonia five months after admission. At necropsy much of the brain was seen to be infarcted. No residual tumour was present. No pheochromocytoma was found in the abdomen or thorax.

Discussion

There is a linear relation between C.S.F. pressure and mean systemic arterial pressure in patients with cerebral tumours (Kety *et al.*, 1948). Raised intracranial pressure can produce disturbances in vasomotor and respiratory function due to ischaemia of the medullary centres (Cushing, 1902; Eyster *et al.*, 1909) with stimulation of the sympathoadrenal pathway. The resulting hypertension, due to catecholamine and perhaps renin release, can be blocked in dogs by spinal cord section or autonomic ganglion blockade by tetraethylammonium chloride (Dickinson and McCubbin, 1963). This is the only known pathway for neurogenic hypertension, and as cerebral tumours are common an excess of urinary VMA should be often found. It is therefore surprising that only one similar case has been previously reported (Evans *et al.*, 1972). Cameron and Doig (1970) reported two patients with infratentorial tumours who experienced marked pheochromocytoma-like symptoms but who did not have excess VMA excretion.

We report this case to emphasize the apparent infrequency of this association and to suggest that a prospective study would probably show further similar cases.

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Excretion of Vanilmandelic Acid (VMA) in Patient with Meningioma

Date	14/9/72	26/9/72	27/9/72	2/10/72	3/10/72	9/10/72	2/11/72	4/11/72	27/11/72
VMA excretion (mg/24 hr)	10.0	8.6	9.2	10.7	10.1	Tumour Excision	5.1	4.6	5.6

Normal = <7 mg/24hr.