Br. J. Surg. 1992, Vol. 79, December, 1268–1274

Metastasectomy

L. C. Barr, A. I. Skene and J. Meirion Thomas

Department of Surgery, Royal Marsden Hospital, London SW3 6JJ, UK

Correspondence to:
Mr L. C. Barr

The literature on metastasectomy abounds in anecdote and retrospective studies of non-randomized patients. In this paper, the published evidence concerning the efficacy of metastasectomy in the lung, liver, brain, gastrointestinal tract and omentum is reviewed to formulate practical recommendations for patient selection and treatment. At some sites metastasectomy can be recommended with little hesitation for more widespread application, but surgery for liver metastases should still be regarded with some reservation.

The idea that surgeons should endeavour to resect distant metastases of malignant neoplasms contains a degree of absurdity. The presence of metastases implies systemic dissemination of disease and the notion that surgery could be of any value in this circumstance, except perhaps in the palliation of some local symptom, might be considered as misplaced enthusiasm. However, metastasectomy has become one of the most common indications for major liver and pulmonary resection in the developed world, and reports of metastasectomy of almost every conceivable cell type from every major organ in the body can be found.

The role of surgery in controlling regional metastases within lymph nodes is well established for tumours such as squamous cell carcinoma of the head and neck, malignant melanoma, testicular teratoma and breast cancer. Lymph node dissection can prolong life by averting involvement of a vital structure such as the carotid artery or trachea, although for diseases such as carcinoma of the breast, in which locoregional disease by itself is rarely fatal, the exact influence of lymph node surgery on survival is still uncertain. The purpose of this paper is to examine the role of metastasectomy for distant metastases (as opposed to regional node metastases) by reviewing the published evidence.

Lung metastases

The first report of pulmonary metastasectomy appears to be that of Barney and Churchill in 1939, who described a patient presenting with a solitary lung tumour in whom a primary renal cell carcinoma was subsequently discovered on routine physical examination[1]. After nephrectomy and a period of observation the pulmonary metastasis was resected; the patient survived for 23 years and died from cardiovascular disease. Alexander and Haight reported a series of patients in 1947 who had undergone resection of solitary lung metastases from a variety of primary tumours[2], and since that time the indications for pulmonary metastasectomy have been extended to include other primary diagnoses and multiple metastases. The morbidity of the operation is low and the operative mortality rates in recent series[3–6] range from zero to 2 per cent. Several reports of long-term survival after pulmonary metastasectomy have appeared[7–9].

Osteogenic sarcoma

The treatment of osteogenic sarcoma was revolutionized in the 1970s by the introduction of chemotherapy using high-dose methotrexate and leucovorin rescue. This discovery, that preoperative chemotherapy could achieve considerable regression of the primary tumour, occurred at the same time as bioengineering developments that allowed *en bloc* resection of the residual tumour with endoprosthetic reconstruction of bone and joints. However, despite its impact in the adjuvant setting, chemotherapy has been unable to cure patients with established lung metastases; the duration of chemotherapy-induced remission is usually <18 months. Osteogenic sarcoma lung metastasis has thus become one of the most important indications for pulmonary metastasectomy in recent years. Approximately two-thirds of patients with relapse in the lung after primary therapy have surgically resectable disease[10]; 5-year survival rates of between 21 and 39 per cent have been reported after metastasectomy, with or without further chemotherapy[4,11–14]. Goorin *et al.*[15] have reported long-term cure of lung metastases from osteogenic sarcoma using surgery alone, but the majority of patients in other series have probably also received cytotoxic chemotherapy, so that the contribution of surgery is difficult to assess. Winkler[16] has commented that thoracotomy is usually better tolerated by children than is a single course of cytotoxic chemotherapy. Surgical metastasectomy for osteogenic sarcoma and other chemosensitive childhood cancers, such as Wilms' tumour or Ewing's sarcoma, may be particularly indicated for relapses after chemotherapy, because the likelihood of a successful secondary response to chemotherapy is reduced. Not surprisingly, the results of surgical treatment of metachronous metastases arising after chemotherapy are inferior to those of multimodality treatment of synchronous metastases[16]. Survival after thoracotomy appears to correlate with the degree of chemotherapy-induced histological necrosis of the resected metastases[8,13,16].

Soft tissue sarcoma

Soft tissue sarcomas in adults also have a propensity to metastasize preferentially to the lung, but in this case the response rates to chemotherapy are inferior to those seen with osteogenic sarcoma or embryonal sarcomas. Surgical metastasectomy is again an important treatment option for these patients, because 5-year survival rates of 10–50 per cent have been reported, although in general the results are inferior to those seen with osteogenic sarcoma[5,6,8,13,17]. Interpretation of the results of this procedure is difficult because the published data on pulmonary metastasectomy come from uncontrolled studies that are greatly influenced by case selection; patients who are most likely to be referred for surgical metastasectomy are those with slowly progressive solitary metastases without evidence of extrapulmonary disease. There are no controlled trials comparing surgery with no treatment, or with localized radiotherapy or chemotherapy, on which to judge the efficacy of surgical metastasectomy. The limited data available[18] on the outcome of untreated pulmonary metastases, however, suggest that these are usually fatal within 2 years. The survival figures after pulmonary metastasectomy are certainly impressive, and there is some evidence that the survival curves may level out after about 5 years, indicating that a proportion of patients are being 'cured'[19]. Repeat operations for recurrent pulmonary metastases may also be valuable[3].

0007–1323/92/121268–07

Renal cell carcinoma

Only a small proportion of patients with lung metastases from renal cell carcinoma have solitary or surgically resectable metastases, probably of the order of 1–3 per cent. Survival rates 5 years after metastasectomy of up to 35 per cent can be achieved[20], with the best results seen in patients with solitary metastases; repeat operations may again have some benefit[21]. Spontaneous regression of pulmonary metastases after nephrectomy is a well known but extremely rare phenomenon; only 67 cases were found in reviews of the world literature from 1928 by Freed *et al.*[22] in 1977 and Fairlamb[23] in 1981. Spontaneous regression is not, of course, synonymous with cure, because some lesions may regress while others simultaneously progress, and regression may be only short lived. Indeed, only 12 of the 67 cases reported have documented 5-year follow-up. It has been pointed out that the likelihood of achieving spontaneous regression is much less than the operative mortality rate associated with nephrectomy; surgery to the primary tumour should probably be avoided in patients with multiple metastases because nephrectomy neither increases survival nor improves the quality of life in these cases[24,25]. For patients with a surgically resectable primary and a solitary metastasis, nephrectomy and metastasectomy is the treatment of choice.

Other tumours

The role of metastasectomy in other tumours is more controversial. Excellent survival figures of >80 per cent at 5 years have been obtained following resection of testicular teratoma metastases, even when active tumour was found within the teratoma deposits after chemotherapy[5]. Van Dongen *et al.* consider that metastasectomy for testicular teratoma is primarily indicated for staging purposes, but it probably also confers some therapeutic benefit[19]. The situation appears to be comparable to para-aortic lymph node dissection after chemotherapy for teratoma, where surgery is useful both for staging and for increasing the likelihood of disease control, presumably because there is a subgroup of patients with residual disease confined to the resected tissues. The situation with malignant melanoma is less encouraging. Resection of pulmonary metastases of melanoma appears to be associated with a universally poor outcome, with virtually no survivors at 2 years, and most authors are reluctant to recommend thoracotomy[8,26]. Patients with lung metastases from carcinomas of the breast or colon may occasionally be suitable for metastasectomy, but this is a relatively uncommon indication[27] because the proportion of these with resectable metastases confined to the lung is only about 1 per cent. Rates of survival at 5 years of 20–45 per cent for such patients can be obtained, however, perhaps reflecting the favourable natural history found in this highly selected group of patients with slowly growing lung metastases and no evidence of disease elsewhere[6,8,13,26]. Despite the difficulty in attributing prolonged survival to metastasectomy or to the natural history of the disease, patients with solitary lung metastases from colorectal carcinoma should certainly be considered for metastasectomy, because the morbidity rate is low and results from published series encouraging, provided there is no concurrent disease at other sites[28,29].

Prognostic factors

A number of authors have attempted to establish selection criteria for pulmonary metastasectomy by identifying factors associated with prolonged survival. Factors generally considered to predict a good outcome after metastasectomy are:

1. Histology other than melanoma[5,8,26].
2. Availability of effective systemic therapy[5,8,13,16].
3. Control of disease at the primary site[30].
4. Small number of metastases[11,13,17,30,31].
5. Complete surgical clearance[5,19,31].
6. Long tumour volume doubling time[19,32,33].
7. Long disease-free interval[13,26,31,34,35].

There is controversy among authors as to the relative significance of these. The importance of the histological type of tumour has already been considered. Patients who tend to do best are those with tumours responsive to chemotherapy, such as testicular teratoma. Patients with melanoma fare badly, and those with carcinoma or sarcoma have intermediate results, osteogenic sarcoma being associated with better survival rates than adult soft tissue sarcomas.

The number and size of lung metastases resected are important prognostic factors in many series (independent of tumour histology), with the best survival rates seen in patients with fewer than four metastases[11,13,17,30,31]. Others have found that surgical resectability rather than the number of metastases is important: if complete surgical clearance can be achieved, the number of lesions resected does not matter[5,19,31]. Patients with unexpected hilar nodal disease or irresectable pleural disease, for example, have a poor prognosis, underlining the importance of performing careful computed tomography (CT) before operation. Control of the disease at the primary site and at other extrapulmonary locations is usually a prerequisite for metastasectomy; Pastorino *et al.*[30] have found that subsequent local recurrence at the primary site is associated with loss of control systemically, presumably because both are an expression of aggressive tumour biology.

A long disease-free interval between diagnosis of the primary and appearance of the first lung metastasis correlates with good survival after thoracotomy in many series[13,26,31,34,35] and this criterion is frequently used in the selection of patients for metastasectomy. However, in other series across a variety of histological types, the disease-free interval was not found to be of prognostic importance. Patients with short disease-free intervals or with synchronous metastases have achieved survival after thoracotomy equivalent to that of those with long intervals[11,17,19,32]. Van Dongen *et al.*[19] have tried to explain this apparent anomaly by postulating that, because the successful establishment of distant metastases is time dependent, some rapidly growing tumours may present early with a solitary metastasis before multiple deposits have had an opportunity to develop and thus benefit from early metastasectomy. This hypothesis seems implausible, and a better explanation may lie in the relationship between disease-free interval and tumour volume doubling time. Tumours with a long disease-free interval tend to be those with long doubling times and thus relatively favourable prognoses. Tumours with a short disease-free interval, on the other hand, may be a mixture of lesions with short doubling times (poor prognosis) and long doubling times (good prognosis) because of the variability of the time to initial diagnosis and time to metastasis within the natural history of a tumour. Joseph *et al.*[18], Holmes *et al.*[33] and Mountain *et al.*[32] have argued convincingly that tumour volume doubling time, calculated from serial chest radiographs, rather than the primary–secondary interval should be used as a selection criterion so that metastasectomy is not denied patients with a long tumour volume doubling time despite a short disease-free interval. Unfortunately, the calculation of tumour volume doubling time is usually impractical because serial radiographs with assessable disease may be unavailable and tumour growth rates can be Gompertzian rather than constant. Whatever the biological explanation, the clinical observation that some patients with synchronous metastases or short disease-free intervals have a good outcome after metastasectomy is certainly important, and the opportunity of metastasectomy should not be denied on this criterion alone.

In summary, pulmonary metastasectomy appears to be a well tolerated procedure that carries a low morbidity rate. It is undoubtedly associated with an occasional long-term cure, and probably affords enhanced survival for a further significant subgroup of patients with a variety of carcinomas and other malignant tumours. The most important criterion for patient selection appears to be that of surgical resectability; if all the disease can be cleared, good survival can be obtained for patients with multiple as well as solitary metastases.

Liver metastases

Liver resection for metastases of colorectal cancer has been pursued vigorously in many centres around the world over the past two decades. Interest in such surgery was kindled by studies of planned relaparotomy for colorectal cancer by Wangensteen in the 1940s and 1950s, in which a number of patients with solitary liver metastases appeared to benefit from liver resection[36]. Subsequent reports of carcinoembryonic antigen-initiated 'second-look' surgery appeared to confirm that some patients with solitary liver metastases achieved prolonged survival following liver resection[37,38]. Although the number of patients benefiting was small, the depressing overall survival rate of this condition fuelled continuing interest. There is now an extensive literature on hepatic metastasectomy that demonstrates that low operative mortality rates can be achieved with subsequent survival figures that appear promising when compared with the overall outlook for patients with liver metastases.

Overall 5-year survival rates following hepatic resection range from 10 to 32 per cent in the major published series[39–57], the higher end of this range tending to contain patients undergoing resection of solitary rather than multiple metastases (*Table 1*). The risk of relapse within the liver or with extrahepatic disease after hepatic metastasectomy is high, many patients presumably having undetected residual disease at the time of surgery. Careful patient selection is thus crucial, requiring CT before operation and arteriography or intra-operative ultrasonography to exclude multifocal liver disease and extrahepatic disease. Nevertheless, the ability of current investigative techniques to detect liver metastases <1 cm in diameter is poor. Herein lies a paradox: more intensive patient selection leads to better results, but a smaller number of individual patients to whom the treatment can be offered.

Prognostic factors

Most authors agree that the extent of liver involvement is an important predictor of outcome following surgical resection. Some have found that the total number of metastases is important, with poor survival seen after surgery for four or more[45,58,59]. Others have disagreed, finding that the number of metastases resected was irrelevant to subsequent survival and that the important factors appeared to be the percentage involvement of liver parenchyma and surgical resectability[43,56,60]. Bilobar *versus* unilobar involvement does not correlate with survival, provided all the disease is surgically resectable[45,56,59,61].

As with pulmonary metastasectomy, there has been debate about the significance of the disease-free interval as a prognostic factor. Hughes *et al.*[61], in a multi-institutional study, found an improved actuarial 5-year survival rate for patients with a primary–secondary disease-free interval >1 year (42 per cent) compared with those with an interval of $\leqslant 1$ year (24 per cent) ($P < 0{\cdot}01$). Many others have found no difference comparing surgery for synchronous *versus* metachronous metastases[43,45,54,56,60]. Bismuth *et al.*[62] have suggested a practical compromise, recommending that a gap of 3–4 months be left between primary surgery and resection of synchronous colorectal metastases. Any subsequent surgery is preceded by intensive restaging investigations to exclude patients with rapidly progressing disease.

The stage of the original primary carcinoma also appears to correlate with survival after metastasectomy, as the 5-year survival rate associated with Dukes' B lesions is about 30 per cent, compared with 20 per cent for Dukes' C; similarly, a narrow margin of clearance at the time of surgery for the primary tumour is associated with a poorer outcome after metastasectomy[48,63]. Such adverse factors should not, however, be regarded as absolute contraindications to metastasectomy.

Table 1 *Survival following hepatic metastasectomy*

Reference	Year	No. of patients	Operative mortality rate (%)	5-year survival rate (%)
Wanebo *et al.*[39]	1978	27	7	28*
Foster[40]	1978	78	5	22
Blumgart *et al.*[41]	1979	9	11	(1 patient)
Logan *et al.*[42]	1982	19	5	(4 patients)
Fortner *et al.*[43]	1983	65	7	30*
Cady and McDermott[44]	1985	23	0	n.k.
Ekberg *et al.*[45]	1986	58	6	16
Adson[46]	1987	141		23
Gall[47]	1987	110	5	32†
Bradpiece *et al.*[48]	1987	24	8	n.k.
Nordlinger *et al.*[49]	1987	80	5	25
Adloff *et al.*[50]	1987	55	2	20
Di Giorgio *et al.*[51]	1989	21	14	(4 patients)
Mentges *et al.*[52]	1989	49	6	11
Scheele *et al.*[53]	1990	226	6	24 (40)‡
Schlag *et al.*[54]	1990	122	4	10
Coppa[55]	1990	42	4	22
Doci *et al.*[56]	1991	100	5	30
Vogt *et al.*[57]	1991	36	0	20

n.k., Not known. *Does not take operative mortality into account. †Excludes patients with incomplete resection margins. ‡Value in parentheses refers to the survival of those with complete resection and clear margins; the value of 24 per cent is deduced from the raw survival data presented for the patients undergoing metastasectomy overall

Objections to hepatic metastasectomy

Some caution is required when interpreting the apparent success of hepatic metastasectomy. Solitary or low-volume liver metastases can be associated with prolonged survival even if left untreated. For example, Wagner *et al.*[64] studied a series of 252 patients with colorectal liver metastases and reported a 21 per cent 3-year survival rate in the 39 with untreated solitary metastases. Goslin *et al.*[65] found a median survival of 2 years in untreated patients with fewer than four liver metastases and Daly *et al.*[66] corroborated this figure in a study of metastases involving <20 per cent of liver volume. The occasional patient may survive beyond 5 years with untreated liver metastases[64,67]. These figures are not dissimilar to many published results of surgical resection for liver metastases[64].

Minimization of operative mortality is essential if liver resection for metastases is to be contemplated, because any late survival benefit could be negated by a perioperative mortality rate of 5–10 per cent. Some published series unfortunately fail to take operative mortality into account when calculating subsequent survival figures, or exclude patients in whom complete surgical clearance could not be obtained at laparotomy, thus tending to give an overoptimistic impression[39,43,47,53,68]. Operative mortality rates range from zero to 14 per cent in the literature, with 5 per cent being a typical figure in recent series. However, it must be emphasized that these results are from specialist units with a major interest in such surgery; if liver resection for metastases is recommended for more general application, a 'learning curve' associated with less impressive morbidity and mortality rates may occur.

Another objection to surgery for liver metastases is that non-surgical methods of treatment, which avoid the problem of operative mortality, may offer a reasonable alternative. Resection of hepatic metastases in patients requiring alleviation of liver symptoms is rarely beneficial, and a better approach is palliative care using analgesics. Hepatic artery infusional chemotherapy in patients with low-volume liver disease appears to be associated with survival rates similar to those obtained in the published series of liver resection. For example, Ekberg *et al.*[69] found a 15 per cent 5-year survival rate after intra-arterial infusion of 5-fluorouracil, and O'Dwyer and Minton[70] reported survivors beyond 5 years using regional chemotherapy with this drug. In a randomized trial of continuous hepatic artery infusion with or without surgical resection for resectable multiple liver metastases, Wagman *et*

al.[71] were unable to demonstrate any improvement in survival gained by metastasectomy.

The majority of patients with colorectal liver metastases have irresectable disease. In the minority who have resectable metastases, particularly those with solitary metastases, there appears to be a subgroup that is genuinely benefited by hepatic resection, as the number of patients surviving beyond 5 years is greater than might be expected for those with untreated equivalent disease[62]. However, the enhanced survival of a few needs to be seen in the context of the lost survival of those suffering premature operative death at a time when they would otherwise have been asymptomatic and able to live for a median of a further 2 years. The case for liver resection has never been verified by a randomized trial and in view of the reservations outlined its place in the management of colorectal carcinoma should still be regarded as uncertain.

Brain metastases

The brain is another frequent site of metastasis for solid tumours, the most common primary being carcinoma of the lung. About 50 per cent of patients with brain metastases have a solitary intracranial tumour, and of these about 50 per cent will be resectable by virtue of surgical accessibility and the general condition of the patient. Surgical resection is an attractive concept, as metastasectomy in the brain is often relatively straightforward and associated with low operative mortality and morbidity rates. Brain metastases tend to be well circumscribed tumours with a surrounding pseudocapsule of reactive gliosis; Cushing and colleagues were able to demonstrate in the 1920s that they could be readily enucleated from surrounding brain tissue[72]. This encapsulating behaviour is the usual pattern of the tumour–host interface of brain metastases even for tumours with very infiltrative patterns of growth in the tissue of origin[73].

In contrast to metastases in the lungs or liver, brain metastases frequently cause distressing and disabling symptoms even when very small, and a major impetus to undertaking surgical resection has been the desire to achieve rapid alleviation of such symptoms. A high percentage of patients undergoing resection of solitary metastases regardless of the primary histological type achieve immediate and prolonged improvement in neurological symptoms; in only about 12 per cent of cases is there a deterioration of performance status. Although many of the available data are retrospective and uncontrolled, and can be criticized because selection bias may have skewed the results, for comparable tumours the palliative benefit of brain metastasectomy appears to be considerably greater than that which can be achieved using radiotherapy or dexamethasone[74]. This finding has been verified by a randomized trial of surgery with postoperative irradiation *versus* irradiation alone for solitary brain metastases, in which a highly significant difference in Karnofsky performance status was found in favour of surgery. The median time that patients undergoing surgery remained functionally independent was 38 weeks, compared with 8 weeks in those receiving radiation alone[75].

In addition to palliation, the surgical treatment of brain metastases also appears to increase survival, probably by forestalling the development of fatal complications such as intracranial haemorrhage or raised intracranial pressure. In the randomized trial of Patchell *et al.*[75], the median survival of 40 weeks for patients undergoing surgery was significantly longer than the 15 weeks for those having radiation alone ($P < 0{\cdot}01$). Some workers have found that patients presenting with metachronous tumours have a trend towards improved survival[76], although others have found no significant difference, admittedly in studies with small numbers[77,78]. Good survival results have been achieved in patients presenting with primary lung cancer and a single synchronous brain metastasis by surgical resection at both locations[78,79]. Long-term survivors beyond 5 years have been reported following excision of metastases from soft tissue sarcoma and from renal cell, breast and colonic carcinoma, sometimes involving more than one craniotomy over a period of time; useful palliation can be achieved even in malignant melanoma[77,79–85].

Patients with multiple metastases may also be cured by metastasectomy, the key factor being complete surgical resectability, as discussed previously for pulmonary and hepatic metastasectomy[86]. The majority of patients with multiple metastases, however, have irresectable disease and should be considered for brain irradiation. Patients with radiosensitive or chemosensitive tumours, such as small cell lung cancer, germ cell tumours or lymphoma, are similarly better treated by brain irradiation and/or systemic therapy. An exception to this rule may be patients with germ cell tumours of the testis who suffer relapse in the brain in the face of combination chemotherapy; because some chemotherapy agents do not penetrate the blood–brain barrier well, surgery may be the better option[86].

In summary, there is good evidence that metastasectomy is superior to irradiation for solitary brain metastases. About 25 per cent of patients with such metastases have surgically resectable lesions, and therefore operation should be recommended more often.

Gastrointestinal metastases

Malignant melanoma frequently disseminates to the gastrointestinal tract, and in autopsy studies gastrointestinal metastases can be found in about 60 per cent of patients dying from this disease. However, only 3–4 per cent of patients with melanoma develop symptomatic gastrointestinal metastases during life, usually presenting with a complication such as obstruction, intussusception, perforation, haemorrhage or, rarely, obstructive jaundice or cholecystitis. Diagnosis before operation may be difficult, but the majority will have evidence of metastatic melanoma at other sites. Klaase and Kroon[87] reported that 30 cases of gastrointestinal metastases developed in a series of 835 patients with melanoma; in only four was the bowel disease the first evidence of dissemination. The most frequent site of involvement is the small bowel, followed by the colon and stomach. Deposits in the stomach classically appear as 'target' lesions at endoscopy, but gastrointestinal metastases may form ulcers, polypoid tumours or infiltrative stenoses[88].

The primary goal of surgical intervention is usually to deal with the relevant surgical emergency. In the majority, simple metastasectomy with resection of involved bowel results in resolution of symptoms; Khadra *et al.*[89] reported that 44 of 56 patients undergoing surgery for gastrointestinal metastases achieved complete relief of symptoms. The median survival after surgery for gastrointestinal metastases[87,89,90] appears to be about 1 year, but a number of survivors beyond 5 years have been reported; the actuarial 5-year survival rate in the series of Klaase and Kroon[87] was 19 per cent. Although the primary goal of this surgery may be palliation, a vigorous attempt to resect all macroscopic gastrointestinal disease is justified because of the possibility of achieving long-term survival for a proportion of patients.

Omentectomy

Omentectomy for carcinoma of the ovary is added to this review for completeness. The rationale behind this procedure, which is usually performed as part of the primary surgical treatment of ovarian cancer before cytotoxic chemotherapy or at planned relaparotomy at the end of chemotherapy, is the concept of cytoreduction. Surgery alone is rarely adequate for this disease except for selected stage IA cancers, and cytotoxic chemotherapy (usually involving platinum-containing regimens) has become the principal treatment for the majority of patients. There are good theoretical reasons for believing that the lower the total tumour cell burden in a patient, the more effective such chemotherapy may be in obtaining complete remission[91,92]. Reducing the tumour cell burden by cytoreductive surgery

before chemotherapy has thus become widely accepted practice and, as the omentum is known to harbour ovarian carcinoma metastases in up to 60 per cent of cases overall and in 20 per cent of clinically uninvolved omenta, omentectomy has been added to the standard operation of total abdominal hysterectomy with bilateral salpingo-oöphorectomy, often in conjunction with multiple peritoneal, diaphragmatic and retroperitoneal lymph node biopsies[93–95]. The usual practice is to remove only the infracolic omentum but, in patients with macroscopic omental involvement, formal omentectomy including the gastrocolic ligament is probably preferable[96].

The concept of cytoreductive surgery to obtain minimal tumour cell burden is attractive, but it is uncertain whether there is evidence to suggest that it works in clinical practice. There is clearly a relationship between the likelihood of response to chemotherapy and the amount of tumour left behind at the time of first laparotomy. For stage I disease, patients undergoing suboptimal surgery appear to have worse survival rates than those undergoing total abdominal hysterectomy, bilateral salpingo-oöphorectomy and omentectomy. For example, Sevelda *et al.*[97] reported a 5-year survival rate of 62 *versus* 84 per cent, respectively, in patients undergoing unilateral salpingo-oöphorectomy compared with those having hysterectomy, oöphorectomy and omentectomy. However, the reason for this difference in survival rate is likely to be understaging of the suboptimal surgery group in this retrospective study and not any direct therapeutic benefit imparted by more radical surgery. For stage III or IV disease, optimal cytoreduction (defined as residual disease <2 cm in diameter) is again associated with better response rates to chemotherapy and improved survival rates in comparison with patients left with disease >2 cm in diameter[98–100]. This effect cannot be attributed to an anomaly of staging and may suggest that cytoreduction is important. An alternative explanation is that the different survival reflects different tumour biology rather than any benefit imparted by surgery, the tumours that prove impossible to clear surgically having an intrinsically worse biological behaviour than those amenable to surgery[101]. This hypothesis is difficult to refute outside a randomized trial, but until such data become available the pragmatic approach is to assume that macroscopic tumour clearance is of therapeutic value and therefore the surgical goal.

The concept of cytoreduction as an adjunct to chemotherapy has led to the next logical step in the treatment of ovarian cancer: second-look laparotomy. The rationale for performing a second operation at the completion of chemotherapy has been partly that of restaging, so that patients with residual disease can continue with further courses of chemotherapy, and partly therapeutic in giving the surgeon a second chance to achieve complete macroscopic tumour clearance[102–104]. Planned relaparotomy gives information of prognostic significance, because patients with secondary residual tumour have a worse outlook than those in complete remission. The therapeutic value of second-look surgery is, however, difficult to determine[101,104], and there is controversy about whether it produces any improvement in long-term survival[103,105,106]. Lawton *et al.*[106] reported 108 patients undergoing planned relaparotomy in whom total macroscopic tumour clearance was possible in 26; the median disease-free survival of the surgically cleared group was 17 months compared with 9 months in the remaining 82, but both groups did badly compared with patients achieving complete tumour clearance at first laparotomy. Redman *et al.*[107] reported 24 patients with residual disease at first laparotomy who had early second-look surgery after three courses of chemotherapy and who underwent debulking to <2 cm residuum; the survival of this group was not significantly greater than that of historical controls with residual disease who did not undergo planned relaparotomy.

Despite these reservations, omentectomy for overt or occult omental metastases should still be considered an essential part of the surgical treatment of ovarian cancer. In early-stage disease it gives valuable staging information and in more advanced disease appears to have some therapeutic benefit as an adjunct to chemotherapy. Planned relaparotomy may be of value as a staging procedure in selected patients, facilitating decisions about second-line chemotherapy. It may also be useful in palliation of symptoms due to bulk disease, but its ability to enhance survival by giving a second opportunity for cytoreduction is still unproven.

Conclusions

The literature on the subject of metastasectomy abounds in anecdote and retrospective studies of non-randomized patients, but a number of confident assertions can still be made. First, metastasectomy is undoubtedly of value in relieving symptoms caused by the local effects of a distant metastasis, particularly those in the brain or gastrointestinal tract, and should be considered the treatment of choice in these situations. Second, there is a subgroup of patients for whom metastasectomy is also a means of prolonging life. For brain metastases this has been demonstrated in a randomized trial; for pulmonary, liver and gastrointestinal metastases it can be inferred from the observation of long-term cures in a significant minority of patients. Third, metastasectomy can be recommended only when it can be achieved with low operative morbidity and mortality rates, as any long-term gain may otherwise be negated by short-term losses. It is for this reason that metastasectomy for lung and brain metastases can be recommended with little hesitation, although resection of liver metastases must still be regarded with some reservation.

References

1. Barney JE, Churchill EJ. Adenocarcinoma of the kidney with metastases to the lung. *J Urol* 1939; **42**: 269–76.
2. Alexander J, Haight C. Pulmonary resection for solitary metastatic sarcomas and carcinomas. *Surg Gynecol Obstet* 1947; **85**: 129–46.
3. Rizzoni WE, Pass HI, Wesley MN, Rosenberg SE, Roth JA. Resection of recurrent pulmonary metastases in patients with soft tissue sarcomas. *Arch Surg* 1986; **121**: 1248–52.
4. Al-Jilaihawi AN, Bullimore J, Mott M, Wisheart JD. Combined chemotherapy and surgery for pulmonary metastases from osteogenic sarcoma: results of 10 years' experience. *Eur J Cardiothorac Surg* 1988; **2**: 37–42.
5. Venn GE, Sarin S, Goldstraw P. Survival following pulmonary metastasectomy. *Eur J Cardiothorac Surg* 1989; **3**: 105–9.
6. Goya T, Tsuchiya R. Surgical resection of metastatic neoplasms of the lung. *Gan To Kagaku Ryoho* 1990; **17**: 771–6.
7. Appelqvist P, Kostianinen S. Multiple thoracotomy combined with chemotherapy in metastatic adrenal cortical carcinoma: a case report and review of the literature. *J Surg Oncol* 1983; **24**: 1–4.
8. Muller MR, Eckersberger F, Klepetko W, Wolner E. Resection of lung metastases: results and prognostic factors. *Zentralbl Chir* 1991; **116**: 15–22.
9. Beattie EJ, Harvey JC, Marcove R, Martini N. Results of multiple pulmonary resections for metastatic osteogenic sarcoma after two decades. *J Surg Oncol* 1991; **46**: 154–5.
10. Huth JF, Eilber FR. Patterns of recurrence after resection of osteosarcoma of the extremity: strategies for treatment of metastases. *Arch Surg* 1989; **124**: 122–6.
11. Maeda H, Nakahara K, Ohno K *et al.* Surgical treatment of pulmonary metastases from osteogenic sarcoma – significance of aggressive resection of bilateral multiple metastases and tumors invading adjacent organs. *Nippon Kyobu Geka Gakkai Zasshi* 1989; **37**: 344–9.
12. Belli L, Scholl S, Livartowski A *et al.* Resection of pulmonary metastases in osteosarcoma: a retrospective analysis of 44 patients. *Cancer* 1989; **63**: 2546–50.
13. Eckersberger F, Klepetko W, Wolner E. Resection of pulmonary metastases: indications, surgical technique, results and prognostic factors. *Wien Klin Wochenschr* 1989; **101**: 69–75.
14. Pastorino U, Valente M, Gasparini M *et al.* Lung resection for metastatic sarcomas: total survival from primary treatment. *J Surg Oncol* 1989; **40**: 275–80.
15. Goorin AM, Delorey MJ, Lack EE *et al.* Prognostic significance of complete surgical resection of pulmonary metastases in

patients with osteogenic sarcoma: analysis of 32 patients. *J Clin Oncol* 1984; **2**: 425–31.
16. Winkler K. Surgical treatment of pulmonary metastases in childhood. *Thorac Cardiovasc Surg* 1986; **34**: 133–6.
17. Roth JA, Putnam JB Jr, Wesley MN, Rosenberg SA. Differing determinants of prognosis following resection of pulmonary metastases from osteogenic and soft tissue sarcoma patients. *Cancer* 1985; **55**: 1361–6.
18. Joseph WL, Morton DL, Adkins PC. Prognostic significance of tumour doubling time in evaluating operability in pulmonary metastatic disease. *J Thorac Cardiovasc Surg* 1971; **61**: 23–32.
19. Van Dongen JA, Hart AA, Jonk A, Postuma HS, Vos A, van Zandwijk N. Resection of pulmonary metastases – results, prognostic factors, reappraisal of selection criteria. *Thorac Cardiovasc Surg* 1986; **34**: 140–2.
20. Tolia BM, Whitmore WF. Solitary metastasis from renal cell carcinoma. *J Urol* 1975; **114**: 836–8.
21. Dernevik L, Berggren H, Larsson S, Roberts D. Surgical removal of pulmonary metastases from renal cell carcinoma. *Scand J Urol Nephrol* 1985; **19**: 133–7.
22. Freed SZ, Halperin JP, Gordon M. Idiopathic regression of metastases from renal cell carcinoma. *J Urol* 1977; **118**: 538–42.
23. Fairlamb DJ. Spontaneous regression of metastases from renal cancer. *Cancer* 1981; **47**: 2102–6.
24. Woodhouse CRJ. Adenocarcinoma of the kidney: review of treatment options. In: Alderson AR, Oliver RTD, Hanham IW, Bloom HJG, eds. *Urological Oncology: Dilemmas and Developments*. Chichester: John Wiley, 1991: 3–11.
25. Johnson DE, Kaesler KE, Samuels ML. Is nephrectomy justified in patients with metastatic renal carcinoma? *J Urol* 1975; **114**: 27–9.
26. Kelm C, Achatzy R, Ritscher R, Wahlers B, Worn H, Kunze WP. Surgery of lung metastases. *Thorac Cardiovasc Surg* 1988; **36**: 118–21.
27. Delaini GG, Dagradi V, Montresor E *et al.* Surgical treatment of pulmonary metastases of colorectal cancer. *Chir Ital* 1985; **37**: 479–84.
28. Muhe E, Gall FP, Angermann B. Surgical treatment of metastases to the lung and liver. *Surg Gynecol Obstet* 1981; **152**: 211–14.
29. Brister SJ, de Varennes B, Gordon PH, Sheiner NM, Pym J. Contemporary operative management of pulmonary metastases of colorectal origin. *Dis Colon Rectum* 1988; **31**: 786–92.
30. Pastorino U, Valente M, Gasparini M *et al.* Lung resection for metastatic sarcomas: total survival from primary treatment. *J Surg Oncol* 1989; **40**: 275–80.
31. Jablons D, Steinberg SM, Roth J, Pittaluga S, Rosenberg SA, Pass HI. Metastasectomy for soft tissue sarcoma: further evidence for efficacy and prognostic indicators. *J Thorac Cardiovasc Surg* 1989; **97**: 695–705.
32. Mountain CT, McMurtrey MJ, Hermes KE. Surgery for pulmonary metastases: a 20 year experience. *Ann Thorac Surg* 1984; **38**: 323.
33. Holmes EC, Ramming KP, Eilber FR, Morton DL. The surgical management of pulmonary metastases. *Semin Oncol* 1977; **4**: 65–9.
34. Putnam JB Jr, Roth JA, Wesley MN, Johnston MR, Rosenberg SA. Analysis of prognostic factors in patients undergoing resection of pulmonary metastases from soft tissue sarcomas. *J Thorac Cardiovasc Surg* 1984; **87**: 260–8.
35. Eilber FR, Huth JF, Mirra J, Rosen G. Progress in the recognition and treatment of soft tissue sarcomas. *Cancer* 1990; **65**: 660–6.
36. Gilbertsen VA, Wangensteen OH. A summary of thirteen years with the second-look program. *Surg Gynecol Obstet* 1962; **114**: 438–42.
37. Pettavel J, Costa J, Douglas P, Besson A, Savary M, de Tribolet N. Surgery in the treatment of recurrent and metastatic cancer. In: Veronesi U, ed. *Surgical Oncology*. Berlin: Springer-Verlag, 1989: 131–41.
38. Sardi A, Nieroda CA, Siddiqi MA, Minton JP, Martin EW Jr. Carcinoembryonic antigen directed multiple surgical procedures for recurrent colon cancer confined to the liver. *Am Surg* 1990; **56**: 255–9.
39. Wanebo HJ, Semoglou C, Attiyeh F, Stearns MJ. Surgical management of patients with primary operable colorectal cancer and synchronous liver metastases. *Am J Surg* 1978; **135**: 81–5.
40. Foster JH. Survival after liver resection for secondary tumors. *Am J Surg* 1978; **135**: 389–94.
41. Blumgart LH, Drury JK, Wood CB. Hepatic resection for trauma, tumour and biliary obstruction. *Br J Surg* 1979; **66**: 762–9.
42. Logan ES, Meier SJ, Ramming KP, Morton DL, Longmire WP. Hepatic resection of metastatic colorectal carcinoma. *Arch Surg* 1982; **117**: 25–8.
43. Fortner JG, Silva JS, Golbey RB *et al.* Multivariate analysis of a personal series of 242 consecutive patients with liver metastases from colorectal cancer. I: Treatment by hepatic resection. *Ann Surg* 1984; **198**: 306–16.
44. Cady B, McDermott WV. Major hepatic resection for metachronous metastases from colon cancer. *Ann Surg* 1985; **201**: 204–9.
45. Ekberg H, Tranberg K-G, Andersson T *et al.* Determinants of survival in liver resection for colorectal secondaries. *Br J Surg* 1986; **73**: 727–31.
46. Adson MA. Resection of liver metastases – when is it worthwhile? *World J Surg* 1987; **11**: 511–20.
47. Gall FP. Resection of liver metastases. *Onkologie* 1987; **10**: 247–9.
48. Bradpiece HA, Benjamin IS, Halevy A, Blumgart LH. Major hepatic resection for colorectal liver metastases. *Br J Surg* 1987; **74**: 324–6.
49. Nordlinger B, Quilichini MA, Parc R, Hannoun L, Delva E, Huguet C. Hepatic resection for colorectal liver metastases: influence on survival of preoperative factors and surgery for recurrences in 80 patients. *Ann Surg* 1987; **205**: 256–63.
50. Adloff M, Arnaud JP, Thebault Y, Ollier JC, Schloegel M. Hepatic metastasis of colorectal cancer: should it be surgically treated? Report of 55 cases. *Chirurgie* 1990; **116**: 144–9.
51. Di Giorgio A, Picchiotti R, Puntillo G *et al.* Radical surgery and loco-regional chemotherapy in the treatment of liver metastases of stomach and colorectal cancer. *Minerva Chir* 1989; **44**: 2065–71.
52. Mentges B, Batz W, Gobel A, Heintz A. Surgical treatment of liver metastases from colorectal carcinoma. *Dtsch Med Wochenschr* 1989; **114**: 1557–61.
53. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 1990; **77**: 1241–6.
54. Schlag P, Hohenberger P, Herfarth C. Resection of liver metastases in colorectal cancer – competitive analysis of treatment results in synchronous *versus* metachronous metastases. *Eur J Surg Oncol* 1990; **16**: 360–5.
55. Coppa GF. Surgical resection for colorectal hepatic metastases. *Bull N Y Acad Med* 1990; **66**: 211–20.
56. Doci R, Gennari L, Bignami P, Montalto F, Morabito A, Bozzetti F. One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinants. *Br J Surg* 1991; **78**: 797–801.
57. Vogt P, Raab R, Ringe B, Pichlmayr R. Resection of synchronous liver metastases from colorectal cancer. *World J Surg* 1991; **15**: 62–7.
58. August DA, Sugarbaker PH, Ottow RT *et al.* Hepatic resection of colorectal metastases. *Ann Surg* 1985; **201**: 210–18.
59. Stehlin JS, De Ipolyi PD, Greeff PJ *et al.* Treatment of cancer of the liver. *Ann Surg* 1988; **208**: 23–35.
60. Adson MA, van Heerden JA, Adson MH, Wagner JS, Ilstrup DM. Resection of hepatic metastases from colorectal cancer. *Arch Surg* 1984; **119**: 647–51.
61. Hughes KA, Rosenstein RB, Songhorabodi S *et al.* Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of long-term survivors. *Dis Colon Rectum* 1988; **31**: 1–4.
62. Bismuth H, Castaing D, Traynor O. Surgery for synchronous hepatic metastases of colorectal cancer. *Scand J Gastroenterol Suppl* 1988; **149**: 144–9.
63. Benjamin IS. Progress in liver resection. *Cancer Topics* 1989; **7**: 54–6.
64. Wagner JS, Adson MD, van Heerden JA, Adson MH, Ilstrup DM. The natural history of hepatic metastases from colorectal cancer. *Ann Surg* 1984; **199**: 502–7.
65. Goslin R, Steele G Jr, Zamchek N, Mayer R, MacIntyre J. Factors influencing survival in patients with hepatic metastases from adenocarcinoma of the colon and rectum. *Dis Colon Rectum* 1982; **25**: 749–54.
66. Daly JM, Butler J, Kemeny N. Predicting tumour response in patients with colorectal hepatic metastases. *Ann Surg* 1985; **202**: 384–93.
67. Wood CB, Gillis CR, Blumgart LH. A retrospective study of the natural history of patients with liver metastases from

colorectal cancer. *Clin Oncol* 1976; **2**: 285–8.
68. Hunt TM, Carty N, Johnson CD. Resection of liver metastases from a colorectal carcinoma does not benefit the patient. *Ann R Coll Surg Engl* 1990; **72**: 199–205.
69. Ekberg H, Tranberg K-G, Lundstedt C. Determinants of survival after intraarterial infusion of 5-fluorouracil for liver metastases from colorectal cancer: a multivariate analysis. *J Surg Oncol* 1986; **31**: 246–54.
70. O'Dwyer PJ, Minton JP. Survival following self-administered chemotherapy for liver metastases. *J Surg Oncol* 1987; **36**: 275–9.
71. Wagman LD, Kemeny MM, Leong L *et al.* A prospective, randomized evaluation of the treatment of colorectal cancer metastatic to the liver. *J Clin Oncol* 1990; **8**: 1885–93.
72. Read RC, Boop WC, Yoder G, Schaefer R. Management of nonsmall cell lung carcinoma with solitary brain metastasis. *J Thorac Cardiovasc Surg* 1989; **98**: 884–91.
73. Barr LC. The encapsulation of tumours. *Clin Exp Metastasis* 1989; **7**: 277–82.
74. Patchell RA, Cirrincione C, Thaler HT, Galicich JH, Kim JH, Posner JB. Single brain metastases: surgery plus radiation or radiation alone. *Neurology* 1986; **36**: 447–53.
75. Patchell RA, Tibbs PA, Walsh JW *et al.* A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990; **322**: 494–500.
76. Badalament RA, Gluck RW, Wong GY *et al.* Surgical treatment of brain metastases from renal cell carcinoma. *Urology* 1990; **36**: 112–17.
77. Torre M, Barbieri B, Bera E, Locicero S, Pieri-Nerli F, Belloni PA. Surgical therapy in lung cancer with single brain metastasis. *Eur J Cardiothorac Surg* 1988; **2**: 336–9.
78. Demange L, Tack L, Morel M *et al.* Single brain metastasis of non-small cell lung carcinoma: study of survival among 54 patients. *Br J Neurosurg* 1989; **3**: 81–7.
79. Magilligan DJ Jr, Rogers JS, Knighton RS, Davila JC. Pulmonary neoplasm with solitary cerebral metastasis. *J Thorac Cardiovasc Surg* 1976; **72**: 690–6.
80. Vaquero J, Martinez R, el Barkani A, Gomez-Angulo JC, Escandon J. Leiomyosarcoma metastatic to the brain with prolonged survival. *J Neurosurg Sci* 1989; **33**: 291–2.
81. Oredsson S, Ingvar C, Stromblad LG, Jonsson PE. Palliative surgery for brain metastases of malignant melanoma. *Eur J Surg Oncol* 1990; **16**: 451–6.
82. Brega K, Robinson WA, Winston K, Wittenberg W. Surgical treatment of brain metastases in malignant melanoma. *Cancer* 1990; **66**: 2105–10.
83. Nakamura O, Matsutani M, Nagashima T, Ueki K, Nakamura M. The treatment of brain metastasis from breast cancer. *Gan No Rinsho* 1989; **35**: 979–82.
84. Guazzo EP, Atkinson RL, Weidmann M, Effeney DJ. Management of solitary melanoma metastasis of the brain. *Aust N Z J Surg* 1989; **59**: 321–4.
85. Pladdet I, Boven E, Nauta J, Pinedo HM. Palliative care for brain metastases of solid tumour types. *Neth J Med* 1989; **34**: 10–21.
86. Jelsma RK, Carroll M. Brain metastasis from nonseminomatous germ cell tumors of the testis: case report and review of the role of surgery. *Neurosurgery* 1989; **25**: 814–19.
87. Klaase JM, Kroon BB. Surgery for melanoma metastatic to the gastrointestinal tract. *Br J Surg* 1990; **77**: 60–1.
88. Plavsic B, Robinson AE. Variations in gastrointestinal melanoma metastases. *Acta Radiol* 1990; **31**: 493–5.
89. Khadra MH, Thompson JF, Milton GW, McCarthy WH. The justification for surgical treatment of metastatic melanoma of the gastrointestinal tract. *Surg Gynecol Obstet* 1990; **171**: 413–16.
90. Garramone RR Jr, Crombie HD Jr. Gastrointestinal complications of metastatic malignant melanoma. *Conn Med* 1990; **54**: 130–2.
91. Bonnadonna G, Fossati-Bellani F, Valagussa P. Adjuvant systemic therapy. In: Veronesi U, ed. *Surgical Oncology*. Berlin: Springer-Verlag, 1989: 200–17.
92. Martin DS. The scientific basis for adjuvant chemotherapy. *Cancer Treat Rev* 1981; **8**: 169–89.
93. Buschbaum HL, Lifshitz S. Staging and surgical evaluation of ovarian cancer. *Semin Oncol* 1984; **11**: 227–37.
94. Steinberg JJ, Demopoulos RI, Bigelow B. The evaluation of the omentum in ovarian cancer. *Gynecol Oncol* 1986; **24**: 327–30.
95. Yazigi R, Sandstad J, Munoz AK. Primary staging in ovarian tumors of low malignant potential. *Gynecol Oncol* 1988; **31**: 402–8.
96. De Re F, Fontanelli R. Cancer of the ovary. In: Veronesi U, ed. *Surgical Oncology*. Berlin: Springer-Verlag, 1989: 768–82.
97. Sevelda P, Vavra N, Schemper M, Salzer H. Prognostic factors for survival in stage I epithelial ovarian carcinoma. *Cancer* 1990; **65**: 2349–52.
98. Fioretti P, Gadducci A, Del-Bravo B, Prato B. The potential of primary cytoreductive surgery in patients with FIGO stages III and IV ovarian carcinoma. *Eur J Gynaecol Oncol* 1990; **11**: 175–9.
99. Bertelsen K. Tumor reduction surgery and long-term survival in advanced ovarian cancer: a DACOVA study. *Gynecol Oncol* 1990; **38**: 203–9.
100. Sevin BU. Intraoperative staging in ovarian cancer. *Baillieres Clin Obstet Gynaecol* 1989; **3**: 13–21.
101. Varma R, Blackledge G. The third Birmingham Gynaecological Cancer Workshop: what are we doing wrong with ovarian cancer? *Br J Cancer* 1990; **61**: 335–6.
102. Krafft W, Konig EM, Schirmer A, Muller U. Second-look operation or second-look laparoscopy for evaluating complete remission of ovarian cancer. *Zentralbl Gynakol* 1990; **112**: 767–71.
103. Sasaki H, Ochiai K, Terashima Y. Significance of second look surgery in the therapy of ovarian cancer. *Gan No Rinsho* 1990; **36**: 1174–8.
104. Lund B, Williamson P. Prognostic factors for outcome of and survival after second-look laparotomy in patients with advanced ovarian carcinoma. *Obstet Gynecol* 1990; **76**: 617–22.
105. Kamura T, Tsukamoto N, Saito T, Kaku T, Matsuyama T, Nakano H. Efficacy of second-look laparotomy for patients with epithelial ovarian carcinoma. *Int J Gynaecol Obstet* 1990; **33**: 141–7.
106. Lawton F, Luesley D, Redman C, Chan KK, Varma R, Blackledge G. Feasibility and outcome of complete secondary tumor resection for patients with advanced ovarian cancer. *J Surg Oncol* 1990; **45**: 14–19.
107. Redman CW, Blackledge G, Lawton FG, Varma R, Luesley DM, Chan KK. Early second surgery in ovarian cancer – improving the potential for cure or another unnecessary operation? *Eur J Surg Oncol* 1990; **16**: 426–9.

Paper accepted 8 June 1992