THORAX

Editorials

Management of the solitary metastasis

Clinicians are commonly confronted by evidence of initial dissemination of cancer in patients with a known primary tumour. This editorial will discuss the various treatment options for the solitary metastasis and in particular those factors that predict a favourable outcome after surgical resection of the metastasis.

Pulmonary metastases

Postmortem studies show that 30% of patients dying of malignant disease have metastatic invasion of the lungs,[1] and in half of these the lung is the only site of distant spread.[2] Life expectancy after detection of pulmonary metastases is about 12 months, and in most cases a solitary metastasis is rapidly followed by others. The appearance of a solitary opacity on the chest radiograph of a patient with cancer represents a metastasis in about 80% of cases, compared with 1% if there is no history of cancer.[3] Patients who can be rendered free of disease at thoracotomy have longer postoperative survival than those with unresectable disease.[4]

The advent of effective chemotherapy led to a phase of treating patients with pulmonary metastases with chemotherapy alone without considering the possibility of surgical treatment. This fashion persisted despite the fact that a consistent 15–30% five year survival rate had been reported in many series over the last 50 years in selected patients undergoing pulmonary metastasectomy for various different tumour types. The survival compares favourably with that expected after resection of a primary lung tumour. Surgical resection was offered previously only to highly selected patients with a solitary metastasis and a long disease free interval. More recently almost identical survival rates after resection have been achieved for patients with multiple lung metastases from carcinomas and sarcomas.[5]

With improved methods of early diagnosis and treatment the number of patients surviving initial treatment to develop pulmonary metastases is increasing. Patients with pulmonary metastases may have no symptoms attributable to the chest, and the metastases are often diagnosed on a routine chest radiograph at a follow up examination. Before resection of pulmonary metastases can be considered, adequate staging investigations must be performed to ensure that the lung is the only site of disease. The emphasis on investigation will vary according to the histological type of the tumour and its propensity to metastasise to different sites.

The distinction between a truly solitary metastasis and a small number of metastases is somewhat artifical. Although the post-resection survival of patients with a single metastasis is better than that of patients with multiple lesions,[6 7] recent studies have shown that patients with five or fewer nodules on the computed tomogram had a longer survival (median 23·8 months) than those with six nodules or more (median 3·6 months), being similar to that of patients with a solitary metastasis.[8] Among patients whose metastases could be completely resected, there was no difference in long term survival between patients with five nodules or more and those with fewer nodules. These data suggest that a limiting factor for the number of metastatic nodules that can be excised completely may simply be the amount of functioning lung tissue that can be preserved. One patient with leiomyosarcoma was reported to be alive with stable disease 46 months after resection of 32 metastases.[8] Post-thoracotomy survival after resection of unilateral pulmonary metastases does not differ from survival after resection of bilateral metastases once the number of nodules has been allowed for, as patients with unilateral disease tend to have fewer metastases. Although there appears to be a predilection for metastases to be located in the right upper lobe,[7] suggested survival advantages for patients with lesions at this site have not been confirmed.[4] Size of metastasis is probably not an independent prognostic factor but does influence survival through its association with potential for complete resection.[6 9]

There has been controversy over whether the disease free interval affects prognosis after resection of pulmonary metastases. Not surprisingly, correlations have been established between disease free interval and tumour doubling time. This has been shown to be a useful means of selecting patients for resection of their pulmonary metastases. Most agree that there is a general relation between growth rate and prognosis for all tumours in which doubling time has been measured, with the possible exception of osteogenic sarcoma.[10] Joseph and coworkers showed that the one year survival for patients with untreated pulmonary metastases with a tumour doubling time of 20 days or less is 11%. For a tumour doubling time of 21–40 days it increases to 45%, and for patients with a tumour doubling time of more than 40 days there is an 86% one year survival. After resection 97% of those with a tumour doubling time of more than 40 days survived one year and 63% survived five years. Patients with a tumour doubling time of less than 20 days did not gain any survival advantage from surgical resection.[11 12] Therapeutic manipulation may prolong the tumour doubling time,[13] and the evidence suggests that if the tumour doubling time of patients with pulmonary metastases can be prolonged by chemotherapy this results in improved survival.[14] The possibility exists that preoperative response to chemotherapy not only may be an indicator of prognosis after surgical resection but also may directly influence the outcome.

It is well established that the disease free interval correlates with survival in certain types of tumour. Patients with pulmonary metastases from soft tissue sarcoma and a disease free interval of more than 12 months have a significantly longer survival (median 26·5 months) than patients with disease free intervals of 12 months or less (median 12·6 months).[8] The prognosis for other cancers, such as tumours of the breast and colon and osteogenic sarcoma, may not be related to the disease free interval, confirming the differences in biological behaviour between histologically distinct tumours. The importance of the disease free interval in patients with soft tissue sarcomas is

seen when pulmonary metastases detected concurrently with diagnosis of the primary tumour are considered. Putnum *et al* found that only 46% of these patients had resectable disease compared with 80% of patients with metastases developing after treatment of the primary tumour. Among patients with resectable metastases, however, post-thoracotomy survival was similar in the two groups.[9]

The results of resection of pulmonary metastases vary according to the different tumour types. Tumours with a tendency to spread initially to the lung are generally associated with a more favourable outcome after resection than patients with metastases from a primary tumour with a tendency towards more widespread dissemination. Favourable primary tumours are osteogenic sarcoma, soft tissue sarcoma, and renal carcinoma. Less favourable are head and neck, colorectal, uterine, and cervical carcinomas; and breast cancer, melanoma, and gastric and oesophageal cancers tend to have the least favourable outcome. The possibility that a solitary lesion might be a new primary lung cancer or a benign lung lesion should always be considered, especially if it appears some time after potentially curative treatment of the original primary tumour. This is particularly relevant to the patient with a primary squamous carcinoma or adenocarcinoma and in these instances the appropriate curative form of resection should be performed. In a study of 142 patients with controlled upper respiratory or gastrointestinal tract cancer and a solitary pulmonary lesion, Allen and Cahan showed that the solitary lesion was a metastasis in only five cases and a primary lung tumour in the other 137.[13]

As most metastases are located subpleurally they are usually palpable and amenable to wedge excision. Prognosis is best when such a limited operation is possible and is progressively less favourable with increasing extent of resection.[7] It is generally accepted that a margin of no more than 1–2 cm of normal lung should be removed at wedge excision to allow for maximal preservation of respiratory function. The possibility of radical radiotherapy with curative intent for a tumour of small volume where resection is not possible should also be considered. For the symptomatic metastasis that proves unresectable radiotherapy may provide effective palliation, but the benefit is usually brief. Adjuvant chemotherapy as part of the initial treatment of patients with limb sarcomas does not influence survival if pulmonary metastases develop later,[5] whether or not these are resected. Adjuvant immunotherapy, using BCG or tumour cell vaccine, is of little value; the role of chemotherapy after resection is still being evaluated. Rather surprisingly, survival after repeated metastasectomies does not significantly differ from that after the first resection, with an expected 20–30% five year survival rate after each operation. Good prognostic factors following a second metastasectomy for soft tissue sarcoma are a disease free interval of more than six months from first resection to second lung recurrence, less than four lesions detected by tomography before the initial resection, and a tumour doubling time of more than 20 days before the initial resection.[16] Repeated thoracotomies would seem to be justified in selected patients and may still result in long term survival.

Brain metastases

As well as being the most common cause of cancer related death in both men and women, lung cancer is the most common source of brain metastases, occurring in 30–50% of patients at necropsy.[17] Almost half the patients have a solitary metastasis only.[18] Untreated, once cerebral metastases are diagnosed they give a median duration of survival of about one month, but the addition of corticosteroid treatment doubles this. The value of whole brain irradiation has been established for symptomatic relief and improvement of neurological function, but mean survival is still only four to six months and long term survival is rare. Many series have shown that patients with a solitary brain metastasis as the only detectable site of disease have a longer survival after surgical resection than would otherwise be expected, and occasional long term survivors have been consistently reported. Such patients with a solitary site of dissemination of their cancer probably constitute a group with an inherently better prognosis as a result of favourable biological factors. Non-randomised trials have suggested that surgery plus postoperative whole brain radiotherapy results in longer survival and a lower rate of local recurrence of solitary brain metastases (from various primary tumours) than radiotherapy alone.[19,20] The trials are, however, open to the same criticism in that patients were considered for surgery because of their more favourable characteristics. In the study by Mandell *et al*, for example, distant metastases were present in only 6% of the patients treated by surgery compared with 49% of those treated with radiotherapy alone.[20]

Recently Patchell and others have shown in a prospective, randomised trial in patients with documented cancer and a single, potentially resectable brain metastasis that patients treated with surgery and radiotherapy survived longer (40 versus 15 weeks) than patients treated with radiotherapy alone.[21] The improvement was due to a reduction in deaths from brain metastases. Moreover, the patients in the surgical group had a better quality of life, as assessed by Karnofsky performance score, and a significantly longer time from treatment to recurrence at the resection site (more than 59 versus 21 weeks). Most patients in this study (37 of a total of 48) had metastases from non-small cell lung cancer.

Another noteworthy finding was that in 11% of patients conditions other than metastatic brain tumour were found on biopsy, including infections and inflammatory lesions. Thus, if resection of what appears to be a solitary brain metastasis on the computed tomogram is not possible because of inaccessibility, a stereotactic needle biopsy may still be worthwhile to help determine management.

Postoperative whole brain radiotherapy has been routinely used as adjuvant treatment after surgical resection but there have been no randomised trials comparing this combination with surgery alone. Radiotherapy seems to improve control of the cerebral disease, but evidence that it improves overall survival is lacking. At the very least adjuvant radiotherapy would appear to prolong time to neurological relapse[22] and there is some evidence that it reduces the risk of any neurological relapse.[20,23] The lack of improvement in survival is due to the high incidence of death from metastatic disease elsewhere. On a cautionary note, it is prudent to consider the risk of radiation induced neurological damage, especially dementia, in patients surviving a year or longer. Age, sex, or histological type of non-small cell lung cancer seem unlikely to influence survival.[22] A short disease free interval from diagnosis of the primary tumour to recurrence in the form of a solitary brain metastasis many carry an adverse prognosis.[23] As with repeated pulmonary metastasectomy, repeat resection of solitary brain metastases is indicated in occasional patients, with second craniotomies and resection resulting in a one year survival of 30%.[24]

Liver metastases

The results of resection of solitary hepatic metastases from primary lung tumours are not encouraging. Although there

Table 1 Selection of patients for pulmonary metastasectomy

Favourable factors
Acceptable operative risk
Lung only site of disease
Primary tumour controlled
Few ($\leqslant 5$) nodules on computed tomogram
Potential for complete resection
Long tumour doubling time
Long disease free interval in certain tumour types
Favourable histological type (for example, osteogenic sarcoma, soft tissue sarcoma, renal carcinoma)
Factors that do not independently influence outcome
Bilateral metastases
Sex
Site
Size of metastasis
Adjuvant chemotherapy at time of initial treatment of primary tumour
Adjuvant immunotherapy
Repeated metastasectomy

Table 2 Selection of patients for cerebral metastasectomy

Favourable factors
Acceptable operative risk
Brain only site of disease
Primary tumour controlled
Solitary metastasis
Potential for complete resection
Longer disease free interval
Factors that do not influence outcome
Sex
Histological type (non-small cell lung types)
Repeated metastasectomy

are reports of long term survival after resection of metastases from various other tumours, notably Wilms, only two cases of liver metastases from lung primaries have been published, and neither patient survived five years.[25]

Conclusions

In conclusion, there is a place for resection of either a pulmonary or a brain metastasis, and sometimes this treatment lengthens survival. Resection of the metastasis is indicated in selected patients whose primary tumours are apparently cured and in whom the presence of metastases at other sites has been excluded after thorough investigation. The main factors to be considered are summarised in tables 1 and 2. The management and outcome after surgery of multiple lung metastases do not vary greatly from that of the truly solitary metastasis, and if all obvious tumour can be resected this offers a 35% three year and 20–30% five year survival rate. If biopsy is performed, a substantial proportion of suspected lung and brain metastases will be found to be benign lesions or, in the former case, a new and potentially curable primary lung cancer. Perhaps most importantly, the possibility of surgical intervention in the patient with cancer that has metastasised to lung or brain as the sole site of disease should be considered more often. Too frequently the nihilistic belief that the appearance of a metastasis in a patient with cancer indicates a hopeless condition has denied appropriate patients the benefit of surgery.

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