



Surgery for widely disseminated breast cancer: prolonged control by excision of metastases

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DECLARATIONS

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MR first suggested reporting our experience with our patient. GJGR was the principal author, but all authors contributed and approved the final version

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Resection of isolated metastases may contribute to both symptom control and prolonged survival even in the presence of widespread disease.

Case report

A 46-year-old premenopausal woman underwent mastectomy and axillary clearance in 1993 for multifocal right breast malignancy. Histology demonstrated an 8 mm grade 1 carcinoma and 10 and 25 mm grade 3 carcinomas. There was no nodal involvement. Hormone receptor status was not assessed but she was prescribed adjuvant tamoxifen for 5 years.

Almost 10 years later, in December 2002, our patient underwent a left mastectomy and axillary clearance for a 23 mm grade 3 invasive ductal carcinoma showing vascular invasion and involving 2 axillary lymph nodes. The carcinoma was only focally ER positive and PR negative, but c-erbB2 strongly positive. She received adjuvant chemotherapy [6 cycles FEC] and chest wall radiotherapy, and in view of the albeit weak ER positivity, she was started again on tamoxifen.

In August 2004 she complained of back pain. An MRI scan demonstrated multiple bone metastases in the cervical and thoracic spine, and there was some spinal cord compression at T3. A good symptomatic response followed palliative radiotherapy to the upper thoracic spine, and this was followed by 6 cycles of docetaxel chemotherapy in combination with trastuzumab, a change in her hormonal treatment from tamoxifen to letrozole, and a 2-year course of bisphosphonate therapy with zoledronic acid infusions. She continued indefinitely on the three weekly infusions of trastuzumab.

The response was maintained for 2 years, but slight nausea and newly abnormal liver function biochemistry led to a CT scan in August 2006. This showed a 9 cm, apparently solitary, lower right liver lobe metastasis in addition to the numerous sclerotic bone metastases. There was no clinical or investigative evidence of disease progression at any site other than in the liver. The liver metastasis was involving both the left and right portal inflows and was considered inoperable. It was decided to continue with trastuzumab but to treat again with docetaxel chemotherapy. She received another 6 cycles and the diameter of the metastasis reduced by more than 50%. It was then considered operable and following an extended right hepatectomy in March 2007, she made an uneventful swift recovery.

Our patient remained symptomatically well until November 2007, when her upper thoracic spine again became painful. An MRI scan showed some improvement in the degree of bone involvement compared with the MRI scan in 2004, but in view of the pain she was retreated with palliative radiotherapy, to good effect. She continued on trastuzumab and letrozole, and remained symptomatically well until June 2008 when she developed headache, dizziness and vomiting, and a CT scan showed an apparently solitary 33 mm left cerebellar metastasis. She underwent craniotomy and gross total resection. This was followed by whole brain radiotherapy, 40 Gy in 20 fractions, and she made a good recovery.

A now 'routine' 6-monthly whole body CT scan in May 2010, showed a new 2.3 cm lesion in the right adrenal gland. PET CT demonstrated that

this was the only significant source of uptake. There was only mild residual activity in the bone metastases and the brain and liver were clear. Adrenalectomy was undertaken in June 2010, histology confirming a 30×20 mm metastasis of poorly differentiated ductal carcinoma with moderate ER and weak PR positivity.

Our patient continues on the trastuzumab and letrozole combination she has now taken for over six years and is currently [April 2011] symptomatically very well and continuing to enjoy a good quality of life, her metastatic bone disease remaining quiescent. She will shortly be receiving her 110th trastuzumab infusion.

Discussion

Our patient has widespread metastatic breast carcinoma. Systemic treatments, together with palliative radiotherapy, have been effective in controlling her metastatic bone disease for over six years, but not effective in preventing the development of isolated metastases involving liver, brain and adrenal gland. Heterogeneity of metastatic disease within an individual patient is well recognized¹ as is differential response to systemic treatments where, for example, soft tissue and bone metastases from breast cancer are more likely than visceral metastases to respond to hormonal drugs.

The rôle of surgery in the management of patients with distant metastases from breast cancer is undergoing reappraisal and Pockaj *et al.* have conducted a comprehensive review of the relevant literature.² Traditionally the indications for surgery in these patients have been restricted to palliation, but there is accumulating evidence that resection and sometimes repeated resection of oligometastatic disease in liver, lung and brain can be invaluable in helping to achieve prolonged disease control in carefully selected patients, particularly as an adjunct to effective systemic treatment. In more recent years there have been reports of improved survival following both resection of distant oligometastatic disease and of the primary tumour.

Palliative surgery has been defined as surgery to relieve symptoms.³ In our patient, the brain and probably the liver metastases were causing symptoms but the adrenal metastasis was not.

As a result, 2 of the 3 operations our patient has undergone in the past 5 years have been of symptomatic benefit, and there can be little doubt that they have been successful in improving both quality and quantity of life.

Our patient is remarkable in that she has undergone successful resection of progressing isolated metastases involving three other organs, while her metastatic bone disease has been kept under control with drugs and radiotherapy. Our experience thus suggests a potential rôle for surgery as more than merely a palliative treatment for carefully selected patients with isolated but far from solitary metastases. Much caution must however be exercised before extrapolating from experience with a single patient.

Our patient's first evidence of visceral involvement was in the liver. The value of liver resection for selected patients with metastatic breast cancer is now well documented.⁴⁻⁶ The majority of these patients had disease confined to the liver, although a small minority had bone metastases as well. Our patient's liver metastasis was initially considered inoperable, but resection became feasible after chemotherapy induced shrinkage. Adam *et al.*'s series⁵ is the largest, and most of their 85 patients had chemotherapy before resection.

Our patient's second isolated metastasis was in the brain. The value of surgery and whole brain radiation for metastatic breast cancer involving brain is also well documented,⁷⁻⁹ but usually the prognosis for these patients remains poor. Our patient has had no further evidence of brain disease almost three years following treatment and it seems probable that the whole brain radiotherapy has been a major factor in achieving this, although useful penetration of trastuzumab through a blood-brain barrier damaged by metastatic disease or radiotherapy may have been contributory. Trastuzumab is thought not to cross the intact blood-brain barrier, explaining why brain metastases are relatively common in patients who are receiving, or have received, otherwise successful treatment. There is now substantial evidence to justify continuation of trastuzumab following treatment for brain metastases in patients whose disease outside the CNS has continued to respond.¹⁰

Our patient's third isolated metastasis was in the adrenal gland, detected on a 6-monthly CT

scan intended primarily for reassessment of her liver. Castillo *et al.*¹¹ documented their experience of laparoscopic adrenalectomy for suspected incidentally discovered isolated metastatic disease involving adrenal glands. Metastatic disease in the adrenal gland was confirmed in 22 of their 32 patients, but only one of these had breast cancer.

Several authors over the past decade have described improved survival in patients with distant metastatic disease following resection of the primary breast cancer. Seven reports have been summarized by Pockaj *et al.*² All the series have however been retrospective and subject to potential bias, and the rôle of such surgery remains controversial. If there is a real benefit, it is possibly explained by the eradication of the source of new distant metastases.

Trastuzumab [Herceptin] is a recombinant humanized monoclonal antibody, given intravenously, that attaches to the HER2 receptor protein on the surface of the cancer cell and affects its growth. It has transformed the outlook for the minority of patients who have HER2 positive breast cancer, in both adjuvant and palliative settings.

The value of continuing trastuzumab in the presence of progressive disease outside the central nervous system is controversial, although improved time to further progression and overall survival was demonstrated in a phase III randomized controlled study.¹² Current National Institute for Health and Clinical Excellence guidelines¹³ recommend discontinuation of trastuzumab when there is disease progression outside the central nervous system, but not if disease progression is within the central nervous system alone. It seems likely that continuing both trastuzumab and the aromatase inhibitor letrozole has played a very important part in achieving prolonged cancer control for our patient, particularly in her bones, despite isolated progressive disease elsewhere.

The improving medium to long term control of metastatic breast cancer consequent on additional effective systemic treatments seems likely to result in an increasing rôle for surgery, and presumably also for stereotactic radiosurgery, for selected

patients with oligometastatic disease. Patients with progressing isolated metastases may derive more than merely palliative benefit even in the presence of disease at other sites, particularly if the latter is stabilized by other treatments. While at present there is no evidence to justify screening investigations to detect other than local recurrence in breast cancer patients on follow-up,¹⁴ recent and future developments in both drug and localized treatments might increase the chance of benefit from diagnosing oligometastatic disease before it becomes symptomatic.

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