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When to Perform Surgery in Stage IV Melanoma Patients?

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In this issue of ONKOLOGIE, Tomov et al. [1] describe a young patient with stage IV melanoma treated with multiple surgical resections of metastatic disease leading to an apparent cure. In daily practice, the majority of stage IV melanoma patients present with multiple unresectable metastatic lesions and survival is generally poor, with 3-year overall survival rates of approximately 15% [2]. There is no systemic therapy for these patients that can be considered standard. In spite of response rates of up to 50% with some biochemotherapy regimens, superiority in terms of survival has never been demonstrated over single or polychemotherapeutic regimens, which by themselves have not been proven to be superior to treatment with dacarbazine (DITC) alone [3]. So the crucial question is how do we identify patients that may benefit from a surgical approach? Clearly the answer is by selecting out patients with the right biology. This biology may be characterised by the presence of oligometastatic disease and we should base our decisions on site(s) and number of the metastases, the presence or absence of certain biomarkers, and a history of slow versus rapid progression of the patients' disease. The patient in this case report is one of numerous, highly selected patients reported in the literature who benefit from an aggressive surgical approach in metastasised melanoma patients.

In general, the two major reasons to perform surgery in stage IV melanoma patients are palliation and cure. Palliation is considered for patients who have surgically accessible metastases that are symptomatic and negatively influencing the quality of life. The value of surgery for palliation is vastly underestimated. Unfortunately many opportunities to achieve local control are missed and systemic therapy or radiation therapy is given in situations where a relatively simple surgical procedure would have provided the simplest and quickest solution. Especially cutaneous, subcutaneous and distant lymph node metastases can cause local problems that can easily and most effectively be dealt with surgically. But also gastrointestinal, adrenal and splenic metastases are known examples in melanoma patients which can lead to signs of obstruction, bleeding and/or pain and good palliation has been described in these patients [4–6]. Also patients with metastases that may cause significant symptoms before the patient dies of the disease might be candidates for palliative surgery. This requires considerable judgement about whether the potential benefits of the proposed surgery outweigh the risks in the individual patient. In this situation the surgeon is trying to protect the quality of life with minimal morbidity and no mortality of the procedure. This difficult decision requires knowledge of the biology of the disease and clinical performance of the patient and is often made in multidisciplinary teams where medical oncologists and radiotherapists are also involved.

Another reason to perform surgery in patients with stage IV melanoma is to aim for a potentially curative resection. This option is not often possible and results may reflect a more favourable biology of the disease, rather than just an independent therapeutic benefit of the surgical procedure. However, several studies have been presented demonstrating 5-year survival rates between 20 and 30% in selected patients with completely resected metastases [7, 8]. Unfortunately, most published data for metastasectomy are from single-institutional series and comparison between different reports is difficult. Morton et al. have reported the results of a multicentre randomised trial in stage IV patients who underwent complete surgical resection [9]. Patients in this trial were randomised to receive adjuvant onamelatucel-L (Canvaxin®) or placebo. Although the trial was stopped after an interim analysis because no effect was demonstrated of the studied drug, important observations could be made. First, selection of patients for surgery in stage IV melanoma is essential, because only patients with 3 or fewer visceral sites who could be treated with complete surgical resections could enter this trial. Second, treatment was uniformly performed in all participating

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centres with minimal morbidity and mortality and an unprecedented 5-year survival of approximately 40% have been demonstrated in the overall study group of 496 patients. It is clear that these survival percentages are the result of multiple selection procedures. But at the same time it must be recognized that an aggressive surgical approach in stage IV patients is justified provided selection is carried out properly [3].

So, what then are the tools to select successfully those patients that may benefit most from surgery? Established diagnostic modalities for initial staging include patient history, physical examination, chest X-ray, abdominal ultrasound or computed tomography (CT) and magnetic resonance imaging (MRI). Whether positron emission tomography (PET) has a role in improving staging remains to be defined in prospective trials, but results are promising [10]. Prognosis depends on the initial site of the metastases because distant skin and subcutaneous lesions (M1a), pulmonary metastases (M1b) and visceral metastases (M1c) have significantly different 1-year survival rates of 59, 57 and 41%, respectively [2]. However, it is important to realise that after 2 and 5 years survival is similar in these different groups and is less than 20 and 5%, respectively. Several factors have been identified as important for prognosis such as serum lactate dehydrogenase (LDH) which characterises poor prognosis in patients when levels are elevated [2]. Also serum 5-S-CD and S-100B protein levels have been demonstrated to be useful to monitor the clinical course and prognosis of patients with malignant melanoma [11]. Essner et al. have described the largest series of 1,574 patients undergoing surgery for metastatic melanoma. They have identified an earlier primary tumour stage (stage I vs. II), the absence of intervening stage III metastases, solitary metastases and long (>36 months) disease-free interval as predictive of survival [12]. So generally, young patients in a good clinical condition with minimal or solitary metastatic disease reflected by normal levels of LDH and long interval between resection of the primary melanoma and presentation of the metastatic disease are good candidates for potentially curative surgical resections in stage IV melanoma patients. The case report presented by Tomov et al. [1] demonstrates that even repetitive surgical procedures can be possible in this situation with a curative intent.

A word of caution at the end seems appropriate. The use of aggressive surgical procedures in all stage IV melanoma patients should be tempered with the knowledge that incomplete resections put patients at increased risk without any proven survival benefit. The ideal therapeutic approach for melanoma patients with (limited) stage IV disease would be complete metastasectomy followed by an effective adjuvant therapy, which remains to be identified. This should be the strategy to focus on for medical and surgical oncologists to work together and improve long-term survival in this clinically difficult group of patients.

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