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- Isolated limb perfusion for soft tissue sarcoma of the extremities
- Isolated limb perfusion for in-transit melanoma metastases
- Head and neck reconstruction with the infrahyoid flap in the era of free flaps
- Perineal reconstruction following extralevator abdominoperineal excision for low rectal cancer
- Breast metastases from ovarian cancer

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CONTENTS

A 3-year report from the Editor-in-Chief

After the position of Editor-in-Chief was assigned to me by the Board of Directors of the Hellenic Society of Surgical Oncology more than 3 years ago, some quite challenging issues were addressed attempting to improve the quality of the Journal.

In the absence of 'Guidelines for Authors' in the past, the articles were far from uniform with regards to the editing. Hence, 'Guidelines for Authors' were defined and published in the Journal.

Further, the Editorial Board was revitalized. Many of the old Editorial Board Members were not active anymore in the field of Surgical Oncology or not interested to continue being in this position. Due to the more demanding and international character of the Journal to which we aspired, a new Editorial Board was formed with experienced scientists and clinicians in the field of Surgical Oncology in Greece, but also of worldwide leading physicians from abroad.

In an effort to improve the quality of the English language in the Journal, Mrs. Eugenia Bolbasis, a native English speaker and graduate in the English language, was so kind as to linguistically review all full manuscripts voluntarily. Unfortunately, this kind offer came promptly to an end one year ago when she died of metastatic cancer.

Moreover, a sponsor was found to fully cover the publishing expenses of the Journal and to ensure the quality of production in exchange for advertisement placements, so that the Journal was not anymore burdensome for the budget of the Hellenic Society of Surgical Oncology.

Despite all these efforts to improve the quality of the Journal, the number of manuscripts submitted for publication was disappointingly low. While in previous years the planned number of three issues per year was not reached (two issues in 2012 and one single issue in 2013), all quarterly issues have been published with immense effort in the last three years. Three issues were devoted for publication of manuscripts based on lectures from the 13th Hellenic Congress on Surgical Oncology and the congress "Secrets of the Therapeutic Strategy for Oesophageal and Gastric Cancer", both held in Thessaloniki. The remaining six issues and the present issue contained forty-four articles altogether. The lacking or minimal contribution of major Greek surgical departments and oncological centers, including those where members of the Board of

Directors, members of the Editorial Board and members of the Society are working, was wearisome. The department where the Editor-in-Chief is employed, the Department of Surgical Oncology at the Medical School of Crete University Hospital, had to supply two thirds of the manuscripts to complete the quarterly issues. The input of all other Greek centers was limited to less than one quarter of the number of published manuscripts. This lack of manuscript submissions was evidently not altered by a substantial call for manuscripts in an issue of the Journal.

One of the initial goals of the Board of Directors was to work towards the indexing of the Journal in Medline, which seemed quite a challenging task for a young journal and which required effort from all members of the Society. Since such an effort was lacking, it seems evident that this goal was never to be reached. Although the expertise and financial assistance were available to further facilitate accessibility to the Journal by electronic appearance of the contents of each issue on the internet, the lack of support of the Society made that the development of such a website was not considered worthwhile.

I would like to warmly wish the new to be assigned Editor-in-Chief plenty of strength and adequate support from all members of the Society to further improve the quality of our Journal. I myself am cordially willing to continue supporting the Journal as desired.

Eelco de Bree
Resigning Editor-in-Chief

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REVIEW

Isolated limb perfusion for soft tissue sarcoma of the extremities

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ABSTRACT

The standard treatment for soft tissue sarcoma of the limbs is wide local excision with histologically negative margins and, in the majority of cases, adjuvant radiotherapy in an attempt to salvage the limb and to preserve its function. In the case of locally advanced tumours this might not be feasible, especially when the tumour is located at the periphery of the limb or tumour infiltration, encasement or fixation of motor nerves, major vessels or bones is present. In these cases amputation might be necessary. Neoadjuvant treatment with hyperthermic isolated limb perfusion may allow for resection with tumour free margins and consequently adequate local tumour control salvage of the limb and its function. In this review, the rationale, technique, indications and outcome of this treatment modality are discussed. When isolated limb perfusion is indicated, the limited availability of the technique, only one centre in Greece providing this treatment modality, should not be a reason to withhold a patient the opportunity of salvage of the limb and its function.

KEY WORDS: soft tissue sarcoma, extremity, isolated limb perfusion

INTRODUCTION

The standard treatment for soft tissue sarcoma of the limbs is wide local excision with histologically negative margins and, in the majority of cases, adjuvant radiotherapy in an attempt to salvage the limb and to preserve its function.[1-3] However, this might not be feasible in the case of a large tumour, especially when located at the periphery of the limb, and when tumour infiltration, encasement or fixation of motor nerves, major vessels or bones is present. In these cases amputation might be necessary Strategies as alternatives to amputation include preoperative radiotherapy and preoperative chemotherapy.

APROACHES TO LIMB SALVAGE IN LOCALLY ADVANCED TUMOURS

Preoperative radiotherapy does not cause adequate shrinkage of the tumour to convert amputation to limb salvage surgery. In a randomized

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trial[4] and in a systematic review,[5] preoperative radiotherapy did not reduce the proportion of patients with positive surgical margins. Regarding the use of preoperative systemic chemotherapy in order to make the tumour resectable with preservation of the limb's function, soft tissue sarcomas are in general considered chemotherapy-resistant. Sarcomas which are chemotherapy-sensitive, including osteosarcoma, Ewing sarcoma, primitive neuroectodermal tumours and childhood sarcomas like rhabomyosarcoma, do not originate from the soft tissues or encountered very rarely.[6-8] Nevertheless, in a meta-analysis of 18 randomized studies,[9] a significant reduction in local recurrences was observed after adjuvant systemic chemotherapy (risk ratio 0.73, p=0.02). Moreover, in a more recent randomized trial,[10] a reduction, although statistically not significant, in the percentage of locoregional recurrences by the use of adjuvant systemic chemotherapy postoperatively was observed. Preoperative when compared to postoperative systemic chemotherapy may have besides the opportunity for shrinkage of the tumour other advantages, such as avoidance of delay in starting systemic treatment due to postoperative complications, early treatment of eventual micrometastatic disease (from which patients may ultimately die), in vivo assessment of the response to chemotherapy and assessment of the histological response, which is a strong prognostic factor. Theoretical disadvantages are potential delay in local disease control, increased risk of postoperative wound complications and, in case of significant or complete histological response, difficulty in histological assessment of the surgical margins and the exact type of soft tissue sarcoma. In the only randomized trial which investigated the value of preoperative systemic chemotherapy,[11] neither the extent of the performed operation was smaller than as initially planned nor was the microscopical irradicality significantly less observed after preoperative systemic chemotherapy. While overall survival and disease-free survival were not altered by preoperative systemic chemotherapy, complete and partial responses were observed in 8% and 20% of the cases, respectively.

Hence, there might be a role for preoperative chemotherapy to reduce the size and the local extent of limb soft tissue sarcomas to convert amputation into limb salvage surgery, but further improvement is required. Improvement of its efficacy may be attempted with a histology driven choice of the chemotherapeutic agents, the use of novel drugs, the combination of chemotherapy with hyperthermia and the use of regional chemotherapy.[6-8] Traditionally doxorubicin with or without ifosfamide is administered during systemic chemotherapy for all histological types of soft tissue sarcoma. During the last decade however, there is trend to choose the drug according to the histological type, because it seems that specific soft tissue sarcoma types are more sensitive to certain drugs. For example, leiomyosarcoma to the combination of gemcitabine and dacarbazine, myxoid liposarcoma to trabectedin, synovial sarcoma to high-dose ifosfamide, malignant peripheral nerve sheath tumour to the combination of ifosfamide and etoposide, undifferentiated pleiomorphic sarcoma to the combination of gemcitabine and docetaxel and angiosarcoma to paclitaxel and docetaxel.[3,6-8] However, standard first-line chemotherapy for soft tissue sarcomas is still based on anthracyclines and the tailored use of drugs has not yet been adapted except in the context of second-line treatment.[1-3] Moreover, administration of novel drugs such as molecular targeted agents has not yet been incorporated in clinical practice. The other two modalities, the combination of hyperthermia with chemotherapy and the application of regional chemotherapy, will be addressed below.

HYPERTHERMIA

The selective effect of hyperthermia on malignant cells and its ability to enhance the efficacy of chemotherapeutic agents make it a valuable adjunct to chemotherapy.[12,13] The direct cytotoxic

effect of heat has been known since ancient times. The father of modern medicine, Hippocrates (470-377 BC), stated in his Aphorisms: "Where drugs do not cure, iron does; where iron does not cure, heat does; where real heat does not cure, cure is impossible". There is an abundance of experimental and clinical evidence to indicate that malignant cells are selectively destroyed by hyperthermia in the range of 41°C to 43°C.[12-16] However, thermal tolerance can be induced by up-regulation of heat-shock proteins, limiting the importance of a direct antitumor effect of heat.[14] Additionally, thermal enhancement of the efficacy of drugs may arise in a number of ways at cellular level.[15] The combination of heat and chemotherapeutic drugs frequently results in increased cytotoxicity over that predicted for an additive effect. The synergism between both kinds of treatment is caused by several factors including increased drug uptake in malignant cells, which is due to increased membrane permeability and improved membrane transport.[12-16] There is also evidence that heat may alter cellular metabolism and change drug pharmacokinetics and excretion, both of which can increase the cytotoxicity of certain chemotherapeutic agents. Additional factors include increased drug penetration in tissue, temperature-dependent increases in drug action and inhibition of repair mechanisms. In many cases, this enhancement of activity of drugs is already seen above 39-40°C.[17] The thermal enhancement varies among chemotherapeutic agents. Some of the agents with the highest thermal enhancement are melphalan, ifosfomide, platinum compounds and doxorubicin.[17]

In a multicenter randomized trial,[18] the beneficial effect of the addition of regional (deep-wave) hyperthermia to systemic chemotherapy has been demonstrated. Three hundred and forty-one patients with a soft tissue sarcoma at high risk for recurrence (≥ 5 cm, grade 2 or 3 and/or deep localization) were allocated to pre- and postoperative systemic chemotherapy with doxorubicin, ifosfamide and etoposide with or without external regional hyperthermia. While overall survival was similar, local progression-free survival was significantly improved by the addition of hyperthermia to the tumour site (p=0.003). The response of the induction therapy was significantly higher when hyperthermia was added (p=0.002), with complete responses in 2.5% versus 0.8% and partial responses in 26.3% versus 11.9% of the cases. In conclusion, there is clinical evidence that hyperthermia increases the efficacy of chemotherapy in soft tissue sarcomas.

REGIONAL CHEMOTHERAPY

Another approach to increase the efficacy of chemotherapy is the regional application of chemotherapy. Through the isolation of the tumour baring area from the systemic circulation it is possible to administer high drug doses to achieve in the target area high drug concentrations and exposure in order to realize better efficacy, while concurrently low systemic drug levels and so avoidance of high and eventual unsupportable systemic toxicity. Moreover, drugs which may have unacceptable and sometimes lethal toxicity when administered in therapeutic doses intravenously may be safely and effectively used in regional therapy. Another advantage of regional chemotherapy is the possibility to combine it with hyperthermia for further enhancement of its efficacy. Examples of regional chemotherapy are (hyperthermic) intraperitoneal chemotherapy, isolated liver perfusion, stop flow chemotherapy and (hyperthermic) isolated limb perfusion.

HYPERTHERMIC ISOLATED LIMB PERFUSION

Technique

The method of isolated limb perfusion is not a new technique. The first isolated limb perfusion using an extracorporal circuit was performed by Creech and Krementz in New Orleans already in 1958.[19] Since then isolated limb perfusion has

been used much more frequently for in-transit metastases of melanoma than as induction treatment for locally advanced soft tissue sarcoma of the extremities. Under general anaesthesia, the major artery and vein to and from the tumour bearing limb are dissected and properly isolated, cannulae are placed in the vessels and connected to a closed extracorporal circuit with a roller pump, oxygenator and a heat exchanger. At the most proximal site of isolated (part of the) limb, the cannulated vessels has to be cleaned from their branches and the superficial collateral circulation of the limb has to be obstructed by a tourniquet or bandage to minimize drug leakage from the isolated limb to the systemic circulation. According to the tumour localization, isolated limb perfusion may be performed from the axillary, brachial, iliacal, femoral or popliteal vessels. The more distal the site of vessel catheterization is, the lower the extent of eventual toxicity to the limb might be. By heating the perfusate, the chemotherapy is performed under hyperthermic conditions, allowing for thermal enhancement of the drugs' activity. The temperature of the circuit and the limb are continuously measured. When the target temperature is reached TNF-α and melphalan are sequentially administered to the circuit. Before the normal circulation is restored at the end of the perfusion, the limb is rinsed with sterile solutions to remove the remaining drug which may otherwise flow subsequently to the systemic circulation and cause in the end systemic toxicity. Approximately 2 months after isolated limb perfusion, the tumour response is assessed and the tumour is (marginally) resected if feasible.[20-22]

Tumour necrosis factor

While isolated limb perfusion was adopted as treatment of choice for in-transit melanoma metastases, the method was initially not well accepted for locally advanced soft tissue sarcoma of the extremities. This justifiable concern was mainly due to the high regional toxicity in combination with the inadequate tumour regression observed after isolated limb perfusion with cisplatin and doxorubicin.[22,23] The introduction of recombinant human tumour necrosis factor alpha (TNF-α) by Lejeune and Lienard revolutionized isolated limb perfusion.[24] The use of TNF-α, after priming of the tumour with subcutaneous administration of interferon-γ, in combination with melphalan during isolated limb perfusion resulted in 21 complete responses in 23 patients treated for melanoma or soft tissue sarcoma, from whom 12 with no response or recurrence after isolated limb perfusion with melphalan only or cisplatin. Systemic and local toxicity were generally mild.

Typically and according to the registered treatment, TNF-α is combined with melphalan, an alkylating agent with increased antitumour activity under hyperthermic conditions. The melphalan dose of up to 100 mg used (10-13 mg/L perfused limb volume) is as high as the dosage used for myleoablation before stem cell transplantation. TNF-α is multifunctional cytokine that plays a major role in innate and acquired immunity, while its binding to certain receptors leads to haemodynamic and antitumour effects.[25,26] The dose-limiting toxicity of systemically administered TNF-α is systemic inflammatory response syndrome (SIRS) with strong hemodynamic effects which may lead eventual to fatal shock.[26] At the same time, only very limited antitumor efficacy has been seen at doses tolerable with intravenous administration.[26] The administration of TNF-α during isolated limb perfusion enables the avoidance of its devastating hemodynamic effects, and it has demonstrated strong synergistic antitumor effects with chemotherapeutic agents in melanoma and sarcoma patients.[24] In the setting of isolated limb perfusion, TNF-α has two distinct antitumour properties that may be related to each other: increased uptake of melphalan into the tumour and selective destruction of tumour neovascularization.[27] In experimental studies, TNF-α has led to increased vessel permeability and decreased interstitial pressure as immediate effects

after administration.[28,29] These early antivascular effects lead to an up to 6-fold–increased uptake of melphalan into the tumour.[30] Late antivascular effects are best demonstrated in angiograms or gadolinium-based magnetic resonance imaging obtained before and after isolated limb perfusion with TNF-α, showing after treatment a complete shutdown of tumour vasculature, which will ultimately result in tumour necrosis. The latter phenomenon is most likely mediated by tumour vessel disintegration and endothelial apoptosis.[31]

Since already relatively small doses of TNF-α in the systemic circulation may result in fatal toxicity, adequate isolation of the limb's circulation is of utmost importance. Therefore, estimation of the leakage rate from the isolated limb to the systemic circulation is essential before TNF-α is administered to the extracorporal circuit. After administration of a radioactive tracer into the isolated limb circulation and continuous monitoring over the precordium with a gamma probe, leakage is detected by increase in radioactivity.[32,33] The leakage rate should be less than 5-10% to allow for safe drug administration.

In the initial studies,[24,34] interferon-γ had been administered subcutaneously the two days before and during isolated limb perfusion because it was thought to increase the number of TNF-α receptors on the tumour cells and consequently to enhance the treatment's efficacy. However, since in a large series the addition of interferon-γ was not associated with an increased response and appeared even to result in increased toxicity, the administration of interferon-γ has been abandoned.[34,35]

Adverse effects of isolated limb perfusion

The adverse effects of isolated limb perfusion can be separated in systemic toxicity, wound and vascular complications and limb toxicity.[36,37] Systemic toxicity of isolated limb perfusion is due to leakage from drugs from the isolated limb to the systemic circulation. Adequate vascular isolation of the limb and leakage monitoring, as discussed above, are essential. Significant leakage may lead to severe haemodynamic effects which may be even fatal. Therefore, when before drug administration a leakage of more than 5-10% is detected, TNF-α should not be used. A small leakage of TNF-α to the systemic compartment is responsible for the fever that is observed in many cases during the first hours.[36] In a large multicentre series,[34] leakage of TNF-α leaded in 3% of the cases to severe haemodynamic effects and severe leucopenia and thrombopenia due to melphalan leakage were observed each in 3% of the cases. Less frequently observed systemic adverse effects included transient increase in hepatic transaminases (9%), transient renal insufficiency (0.5%) and acute respiratory distress syndrome (0.5%). Complications of the wound do not differ from that seen in other clean operations. Vascular complications as bleeding, pseudo-aneurysm, thrombosis and stenosis are rarely seen in experienced centres.[36]

Regarding the locoregional toxicity, Wieberdink et al[38] proposed a limb toxicity classification already some decades ago (Table 1). Almost in all cases some degree of toxicity to the limb is recorded. In a multicentre study,[34] 92% of the cases grade II or III toxicity was observed and in 2-7.5% the toxicity was of grade IV, while in 0.5% amputation was required for grade V toxicity of the limb. Transient paraesthesia and transient motor neuropraxia occurred in 20% and 8% of the patients,

Table 1. Classification of locoregional toxicity after isolated limb perfusion according to Wieberdink[38]

Grade	Extent of reaction
I	No subjective or objective reaction
II	Slight oedema and/or erythema
III	Marked erythema and/or oedema with some blistering; slight impairment of motility
IV	Extensive epidermiolysis and/or obvious damage to deep tissues, causing definite functional disturbances; threatening or manifest compartment syndrome
V	Reaction that may necessitate amputation

respectively. Long-lasting (mostly peroneal nerve) motor neuropraxia was seen in 3% of the patients. In another large series,[39] local toxicity was absent or mild (grade I and II) in 76% of cases, while grade III and IV toxicity were observed in 21% and 2% of the cases, respectively. No treatment-related amputation had to be performed. Perioperative mortality is 0-0.5%.[34,36,37,39] Whereas development of a compartment syndrome in the limb due to oedema requires fasciotomy, some centres prefer to perform prophylactic fasciotomy during the initial procedure.

Resection after isolated limb perfusion

The purpose of isolated limb perfusion is down staging of the tumour by shrinkage of the tumour, making the tumour less tethered to adjacent structures and the presence of less viable cells at its invasion front.[40] Resection of the tumour remnant is usually performed after approximately two months, allowing for sufficient down staging of the tumour. If feasible, tumour resection should be performed as wide or compartmental resection similar to otherwise performed for extremity soft tissue sarcoma.[21] Since isolated limb perfusion leads to distinct response patterns with devitalization of tumour margins, close or positive margins at critical structures may be acceptable. Nevertheless, marginal resections of tumour remnants for minimal functional impairment after isolated limb perfusion are associated with higher local recurrence rates.[41]

In a study[42] on the histological effect of various neoadjuvant treatments for soft tissue sarcoma, isolated limb perfusion showed the strongest effects at the tumour periphery. It increased the median thickness of the fibrous capsule from 0.2 mm to 0.6 mm and the median thickness of the peripheral reactive zone from 0.7 mm to 1.7 mm. The extent of histopathological regression shows a correlation with capsular integrity and width. Thickening of these layers allowed for an increased integrity of the fibrous capsule at resection (77% versus 35%), while the surgical margins were improved because of the elimination of viable tumour cells in the fibrous capsule.

Treatment efficacy

Isolated limb perfusion was introduced into the therapy of soft tissue sarcomas to avoid amputation in the setting of limb-threatening extremity tumours. Consequently, the most frequently reported endpoints of isolated limb perfusion studies are limb salvage and pathologic response. Impact on overall survival is not being expected since it is definitely a locoregional treatment. To date, no randomized trial comparing isolated limb perfusion with other treatment modalities has been performed in patients with locally advanced soft tissue sarcoma of the extremity. Therefore, only cohort studies are available for assessment of the efficacy of this method. The largest cohort study of isolated limb perfusion with TNF-α and melphalan,[34] which led to the approval of TNF-α by the European Medicines Agency, included 189 patients with locally advanced primary or recurrent soft tissue sarcoma of the limbs who were candidates for amputation. Most of the patients had high grade and large tumours. In 25 patients who had concurrent systemic metatastases isolated limb perfusion with TNF-α and melphalan was used as a palliative treatment. In this multicentre study, (clinical and pathological) complete and partial responses were obtained in 29% and 53% of the cases, respectively. This resulted in a limb salvage rate of 82%. After a median follow-up period of 22 months, 36% had presented with metachronous metastases and 27% had died. A number of subsequent cohort studies[22,41,43-47] reported (nearly) complete responses of 17% to 47% and partial responses of 30% to 56%, resulting in a limb salvage rate of 78% to 96%. The most important criticism of these trials is that isolated limb perfusion with TNF-α and melphalan was used to treat not only amputation candidates but also patients who required resection with major functional impairment, including tumours with fixation to or invasion into major neurovascular

structures and/or bone. The endpoint of limb salvage remains controversial with respect to the definitions of 'candidate for amputation', 'mutilating surgery' and 'resection with major functional morbidity'. Although large high-grade soft tissue sarcomas frequently already exhibit significant central necrosis, the extent of necrosis and fibrosis in a resected specimen may be reliably used to estimate the efficacy of this neoadjuvant treatment.[48]

Since the primary goal of isolated limb perfusion is limb salvage, only a few studies have documented oncological outcome data. Five-year local disease-free survival has been reported from 73% to 87%.[44,45,49] The 5-year metastasis-free survival of approximately 50% demonstrates the aggressive behaviour of sarcomas selected for isolated limb perfusion.[45]

Isolated limb perfusion with TNF-α and melphalan is also an excellent palliative procedure that provides tumour control and limb salvage for the short survival of patients with metastasized, very bulky, limb-threatening tumours of the extremity.[36,50]

Comparison with other treatments

Isolated limb perfusion has never been directly compared with other adjuvant treatment options such as radiotherapy and chemotherapy, with or without hyperthermia. The reasons are the low incidence of limb-threatening soft tissue sarcomas, the presence of other tailored treatment strategies and the low availability of isolated limb perfusion with TNF-α.

The low availability is caused by the fact that TNF-α has never been approved in the United States, while the pharmaceutical company that produces recombinant human TNF-α (Boehringer-Ingelheim, Germany) licenses a centre to use its product for isolated limb perfusion only after approval of the isolated limb perfusion technique at site visitation. In Greece, only one centre (the Department of Surgical Oncology of the Medical School of Crete University Hospital) has received such a license to perform this treatment modality.

The combination of tumour resection and (neo) adjuvant radiotherapy, the current, scientifically established therapy for the soft tissue sarcoma of the extremities, results in a 5-year local disease-free survival of 89% to 92%.[51,52] It should be noted, however, that isolated limb perfusion is typically chosen for large, high-grade, deeply located soft tissue sarcomas, while the surgery and radiotherapy trials included also smaller, superficial and low grade tumours with obviously a more favourable biological behaviour.

In a prospective trial,[53] concurrent preoperative intense systemic chemotherapy and radiotherapy followed by surgery for high-grade soft tissue sarcomas led to a 17% local failure rate. In another study,[54] short preoperative systemic chemotherapy and surgery, with the addition of preoperative or postoperative radiotherapy at discretion of the treating physician, was associated in a 5-year local disease-free survival of 94% in high-grade extremity soft tissue sarcomas. In another prospective study,[18] perioperative systemic chemotherapy with regional (deep-wave) hyperthermia, surgery and postoperative radiotherapy resulted in 4-year local disease-free survival of 82% in patients with extremity soft tissue sarcomas. As already mentioned, proper comparison of the results of these multimodality treatments with those of isolated limb perfusion is biased by patient selection and availability of techniques.

Evolving treatment modifications

Although the complications and toxicity of isolated limb perfusion with TNF-α and melphalan were already acceptable, the technique has evolved over time to decrease further the incidence of adverse effects. While initially the aimed tumour tissue temperature was 40-40.5°C, currently the limb circuit is heated until a tumour temperature of 38 to 39.5°C. The initial target temperature was based on the thermal enhancement of the drug's activity which seems to occur above 40°C[17,55] and the unacceptable regional toxicity at a temperature above 40.5°C.[56,57] However, it appears that with a

tumour temperature of 38 to 39.5°C the response rates are not impaired, while regional toxicity is decreased.[56,57] Therefore this mild hyperthermia, which clinically already results in a temperature rise of 4 to 5°C in the limb, is generated before TNF-α and melphalan are administered to the limb circuit.

Reduction of the TNF-α dose has been applied to decrease further the change of severe haemodynamical adverse effects. Initially the dose of TNF-α was empirically chosen as 3 mg for arm perfusions and 4 mg for the leg perfusions. In a randomized trial,[43] lower dosages of TNF-α were not inferior to high-dose TNF-α with respect to tumour responses, the achievement of negative surgical margins, limb salvage rate and local tumour control. Contrarily, systemic toxicity was decreased for lower dosages. Currently most centres use TNF-α dosages of 2 mg for the lower and 1 mg for the upper extremities.

Moreover, shortening of the limb perfusion time may decrease toxicity and costs. In the initial trials,[34,44] melphalan was injected into the limb circuit 30 minutes after TNF-α, and the cumulative perfusion time was 90 minutes. A comparative study[44] demonstrated that the perfusion time may be reduced to 60 minutes without the treatment outcome being compromised. The standard perfusion time is currently 60 to 75 minutes, and melphalan is administered 15 minutes after TNF-α.

As already mentioned, minimizing the limb volume that is perfused may result in less locoregional toxicity.[21] This can achieved by choosing the vascular access for establishing the limb circuit as close to the tumour as possible. Nevertheless, direct perfusion of the tumour-feeding vessels has to be ensured. Moreover, distantly located vascular cannulation (e.g. femoral or popliteal vs. iliac and brachial vs. axillary) allows easier and more reliable separation of the limb circulation from the systemic circulation. This results in reduction of drug leakage to the systemic compartment and subsequent less systemic toxicity. Segmental perfusion by exclusion of the extremity distant of the tumour by the use of an Esmarch bandage may prevent toxicity to the smaller and more vulnerable muscles of the foot and the hand.[21]

Whereas radiotherapy, before or after surgical resection, is a part of the standard treatment for extremity soft tissue sarcoma, the application of radiotherapy before or after isolated limb perfusion and tumour excision is associated with increased long-term toxicity, including joint stiffness, fibrosis and bone fracture.[44] In a multivariate analysis,[45] postoperative radiotherapy did not improved local disease-free survival in such a cohort of patients. Hence, adjuvant radiotherapy may be omitted to avoid toxicity in patients with negative resection margins at surgery after isolated limb perfusion.

CONCLUSIONS

The currently used treatment schedules of isolated limb perfusion with TNF-α and melphalan for locally advanced soft tissue sarcoma of the extremities are highly effective and associated with low toxicity. Because of the high pathologic response rates, the high limb salvage rate and the improved surgical margins after isolated limb perfusion with TNF-α and melphalan, the indication for performing this treatment should be evaluated for primary and recurrent tumours if infiltration, encasement, and fixation of motor nerves, major vessels, or bones are present as well as for patients who are expected to suffer from relevant (acute or long-term) toxicity from other treatment modalities such as preoperative chemotherapy or irradiation. Hence, this treatment modality should not only be considered as potential therapy when other treatment options are not feasible or have failed. Finally, isolated limb perfusion with TNF-α and melphalan might be also used as a palliative treatment for patients with highly symptomatic locally advanced soft tissue sarcoma of the extremities and concurrent metastatic disease, before or in between courses of systemic chemotherapy. Unfortunately, isolated limb perfusion is not widely available, for example

in no more than three centres in the Netherlands and in only one centre in Greece. When isolated limb perfusion is indicated, the limited availability of the technique should not be a reason to withhold a patient the opportunity of salvage of the limb and its function.

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REVIEW

Isolated limb perfusion for in-transit melanoma metastases

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ABSTRACT

Isolated limb perfusion with melphalan with or without TNF-α is a well-established and effective treatment for inoperable melanoma metastases of the extremities, across the entire range of metastases from subclinical disease to bulky lesions, with a complete response rate of 50-90%. Such a response is durable in half of these individuals. Half of the patients with a complete response survive for ten years, most with an excellent quality of life. In patients who continue to develop in-transit metastases, perfusion can delay and diminish subsequent limb recurrence. This article reviews the technique, results and other aspects of this sophisticated form of treatment.

KEY WORDS: melanoma, in-transit metastases, extremity, isolated limb perfusion

INTRODUCTION

Creech et al[1] at Tulane University in New Orleans were the pioneers who developed isolated limb perfusion. In 1958, they described a 76-year old man with an extensive melanoma recurrence of his leg in whom a complete response was obtained. The man remained free of disease and died 16 years later from another cause. Subsequently, isolated limb perfusion became a well-established treatment option for inoperable melanoma metastases of the extremities. Perfusion exploits the ability of normal tissues in the extremities to tolerate higher drug concentrations than the bone marrow and the vital organs. The rationale is that melanoma is sensitive to cytotoxic drugs, but the disease requires a higher dose than is customary in other types of cancer. In the isolated limb, drug concentrations of up to 20 times the level that would be tolerated in the rest of the body may be reached.[2] Therefore, isolated limb perfusion with a high dose of cytotoxic medication may achieve regional tumour control without major toxicity to the normal tissues of the limb and without exposing the bone marrow and the vital organs to high drug concentrations, and thus avoiding systemic toxicity. This is achieved by isolating the limb from the body's circulation and establishing

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a separate oxygenated and heated extracorporeal blood circulation powered by a pump as described in the previous article on hyperthermic isolated limb perfusion for soft tissue sarcomas of the extremities.[3] In melanoma, hyperthermic isolated limb perfusion is a particularly useful technique for patients with in-transit metastases.

IN-TRANSIT METASTASES FROM MELANOMA

In-transit metastases are metastases that occur in the lymph vessels in the skin or subcutaneous tissue, in between the site of the primary melanoma and the regional lymph node basin. These lesions are typical for melanoma and occur in 5-8% of the high-risk patients, i.e. those with thick melanomas and/or regional lymph node metastases.[4] When the distance between the skin or subcutaneous metastasis and the site of the primary lesion is less than 2-3 cm, it is called a satellite lesion instead of an in-transit metastasis, but in fact it represents the same way of tumour cell dissemination. Although the majority of patients with extensive in-transit metastases of the limb will die from their disease, one should aim for cure if staging shows no metastases elsewhere. Nevertheless, approximately half of the patients are alive after more than two years and the poor quality of life caused by these multiple lesions (pain, haemorrhage, ulceration, odor, etc.) necessitates sufficient treatment of these lesions.[5,6]

The initial treatment of satellite and in-transit metastases consists of complete surgical excision.[4,6,7] When located on the limb, radical surgery with amputation for such regional disease does not appear to improve survival.[7] Since in-transit metastases tend to recur at other sites of the same region, repeated excisions are usually required. However, when the in-transit metastases have become numerous and cover a large area, treatment with local excisions will not be possible anymore. Unfortunately, treatment options such as destruction with laser, local immunotherapy, vaccinations, radiotherapy and conventional systemic chemotherapy and immunotherapy have not been successful in the past.[9-23] At present, electrochemotherapy (the use of bleomycin in combination with the application of electric current over cutaneous or subcutaneous lesions) has produced some promising results,[24-27] but is not considered standard therapy. In a recent large multicenter study,[28] 394 lesions were treated with electrochemotherapy in 114 patients. Complete response was observed in 58% of the lesions and the treatment was well tolerated. However, the follow-up was too short for assessment of locoregional tumour control and only a limited number of visible lesions can be treated with this method.

Regional chemotherapy provides the opportunity to treat a large number of lesions on the entire limb and not only those that are evident but also the smaller ones that would become evident later. Through the isolation of the tumour baring area from the systemic circulation it is possible to administer high drug doses to achieve in the target area high drug concentrations and exposure in order to realize better efficacy, while concurrently low systemic drug levels and so avoidance of high and eventual unsupportable systemic toxicity.[4,6,7] Moreover, drugs which may have unacceptable and sometimes lethal toxicity when administered in therapeutic doses intravenously may be safely and effectively used in isolated limb perfusion. Another advantage of regional chemotherapy is the possibility to combine it with hyperthermia for further enhancement of its efficacy.

HYPERTHERMIC ISOLATED LIMB PERFUSION

Indications

Isolated limb perfusion can be considered in patients with numerous in-transit metastases or frequently recurring in-transit metastases, but also in patients with an inoperable primary or locally recurrent melanoma.[7,29] The general condition of the patient should be assessed and the surgeon

should be aware of concomitant diseases, allergies, and medication. A detailed examination of the skin, the subcutaneous tissues and the regional node field is performed, and the arterial blood supply to the limb is assessed.

In a study of 202 patients combining data from two Dutch centres, the complete response rate in patients over 75 years of age was 56% compared to 58% in younger patients.[30] Approximately half of the patients with a complete response achieved long-term local regional disease control in either age category. Although the hospital stay was somewhat longer in the older patients, acute toxicity, postoperative complications and long-term morbidity were not related to age. The conclusion was that older patients can safely undergo perfusion and profit as much as younger people. Therefore, advanced age is not necessarily a contraindication for isolated limb perfusion.

The presence of regional dissemination should be confirmed by pathology examination. The stage of the disease should be determined and the combination of whole body FDG PET/CT and MRI of the brain is reasonable for the purpose.[7] The finding of metastases elsewhere may change the treatment plan. Systemic therapy should then be contemplated, particularly now that new drugs are available that have been shown to improve survival. However, the presence of distant melanoma metastases does not preclude isolated limb perfusion. Adequate palliation is often achieved in patients with symptomatic but unresectable locoregional limb involvement.[31,32] In particular, palliative isolated limb perfusion should be considered in patients with distant cutaneous or subcutaneous metastases or distant lymph node metastases as they often survive for more than a year.[7]

Arteriography can be performed if the arterial blood supply appears questionable. Perfusion is not feasible if there is complete obstruction of the main artery of the limb. Other absolute contraindiactions include diabetes with serious peripheral vascular disease and children with open epiphyseal plates. Relative contraindications are prior radiotherapy, a large superficial tumour with major tendon involvement and a wound or ulcer with serious infection.[7]

Technique

The procedure is performed under general anaesthesia. Epidural anaesthesia is hazardous in a patient who is to be fully heparinised. It also induces vasodilatation and predisposes to leakage of blood from the systemic circulation to the perfusion circuit, and for these reasons is not recommended. The major artery and vein to and from the disease bearing limb are dissected and properly isolated, cannulae are placed in the vessels and connected to a closed extracorporal circuit with a roller pump, oxygenator and a heat exchanger.[4,6,7] The cannulated vessels have to be cleaned from their branches and the superficial collateral circulation of the limb has to be obstructed by a tourniquet or bandage to minimize drug leakage from the isolated limb to the systemic circulation. For in-transit metastases, isolated limb perfusion is performed from the external iliacal or the axillary vessels, since it represents disease of the entire limb. If not already performed previously, regional lymph node dissection is routinely indicated for this regionally disseminated disease. This is in contrast with the case for soft tissue sarcoma. Brachial, femoral or popliteal vessels may be accessed for the treatment of inoperable primary or locally recurrent melanoma. The leakage rate from the isolated limb to the systemic circulation is estimated after administration of a radioactive tracer into the isolated limb circulation and continuous monitoring over the precordium with a gamma probe; leakage is detected by increase in radioactivity.[33,34]

The limb is warmed up by a heating blanket and heated perfusion fluid. The temperature of the circuit and the limb are continuously measured. When the target temperature is reached the cytotoxic agent, usually melphalan with or without tumour necrosis factor (TNF-α), is administered to the circuit. Before the normal circulation is

restored at the end of the perfusion, the limb is rinsed with sterile solutions to remove the remaining drug which may otherwise flow subsequently to the systemic circulation and cause in the end systemic toxicity. [4,6,7] In contrast to cases of soft tissue sarcoma, surgical excision of the tumour is not planned. However, persistent disease may be excised when feasible.

Temperature

At the time the vessels are accessed, the limb is typically cool. This may result in vascular constriction in the skin and subcutis and consequently lower drug distribution to the target tissue. By wrapping the limb in a heating blanket and heating the perfusate the chemotherapy can be performed under normothermic or mild hyperthermic conditions. The tissue temperatures of the limb are kept between 37°C and 38°C ('controlled' normothermia) or between 39°C and 40°C (mild hyperthermia) during the procedure. As discussed in our article on hyperthermic isolated limb perfusion for soft tissue sarcoma,[3] hyperthermia has a selective toxic effect on malignant cells and the ability to enhance the efficacy of chemotherapeutic agents. While malignant cells are selectively destroyed by hyperthermia in the range of 41°C to 43°C, thermal enhancement of the efficacy of drugs may arise at lower temperatures. Since limb temperatures of more than 40°C are associated with increased local toxicity of isolated limb perfusion with cytotoxic agents and limb temperatures of less than 39°C with decreased response rates, the optimal limb temperature is apparently 39°C to 40°C.[6,7]

In this way the direct cytotoxic effect of heat has not been exploited. To utilize the direct cytotoxic effect of heat, a double perfusion schedule has been tested in the Netherlands Cancer Institute with a 2-hour true hyperthermic perfusion with tissue temperatures between 42°C and 43°C without melphalan, followed by normothermic perfusion with melphalan at regular dosage one week later.[35] The hypothesis was to kill cells in the hypoxic parts of the tumors with the hyperthermia and the rest of the lesions with the melphalan in the subsequent week.[36] With this sequential schedule, both hyperthermia and melphalan were given at the maximum dose without encountering the substantial toxicity that simultaneous treatment would have caused. With this approach, a high complete response rate (63%) and a low limb recurrence rate (27%) were seen in seventeen patients with extensive, recurrent melanoma.[37] The morbidity was mild. This regimen could be considered as an alternative to perfusion with the combination of melphalan and TNF-α in patients with extensive or bulky disease.

Drugs

L-phenylalanine mustard (melphalan) is the standard drug used.[7] Phenylalanine has a key role in the synthesis of melanin. Incorporation of melphalan into them leads to destruction of melanoma cells. The dosage of the drug is adjusted to the requirements of the individual patient. The melphalan dose is usually based on the volume of the extremity, which can be determined using a water reservoir or calculated after multiple measurements of the limb's circumference. Parameters such as gender and obesity may lead to adjustments in the dose. The standard dose is 10 mg/L perfused tissue for the lower limb and 13 mg/L for the upper limb.[2]

The addition of TNF-α to melphalan may be beneficial.[29] As discussed in the article on hyperthermic isolated limb perfusion for soft tissue sarcoma,[3] TNF-α has two distinct antitumour properties that may be related to each other: increased uptake of melphalan into the tumour and selective destruction of tumour neovascularization.[38] In experimental studies, TNF-α has led to increased vessel permeability and decreased interstitial pressure as immediate effects after administration.[39,40] These early antivascular effects lead to an highly increased uptake of melphalan into the tumour.[41] Late antivascular effects after treatment consist of destruction of tumour vasculature, which will ultimately result in tumour

necrosis. Since already relatively small doses of TNF-α in the systemic circulation may result in devastating hemodynamic effects and fatal toxicity, adequate isolation of the limb's circulation and monitoring of the leakage rate from the isolated limb to the systemic circulation are essential.

The use of other agents has been investigated, including cisplatin, vindesine, DTIC, fotemustine, interleukin-2, and lymphokine-activated killer cells, but only actinomycin (in combination with melphalan) has been used in a few centers.[42-50]

Adverse effects of isolated limb perfusion

The adverse effects of isolated limb perfusion are discussed in the article on hyperthermic isolated limb perfusion for soft tissue sarcoma.[3] In brief, they can be separated in systemic toxicity, wound and vascular complications and limb toxicity.[51] Regarding the regional toxicity, Wieberdink et al.[52] proposed a limb toxicity classification already some decades ago. The adverse effects range from commonly observed oedema and erythema to functional disturbances and compartment syndrome and eventual to the rare case (<1%) of local reactions that necessitate amputation. Whereas development of a compartment syndrome in the limb due to oedema requires fasciotomy, some centres prefer to perform prophylactic fasciotomy during the initial procedure. While the oedema and erythema subside over a period of 2–3 weeks, a tan discoloration of the limb gradually disappears over the course of several months. There appears to be no relationship between limb toxicity and tumour response to the treatment.[53] Thus, there is no reason to push the drug dose to the limit of tolerable morbidity.

The most important risk factors for severe acute regional toxicity are tissue temperatures above 40°C, a high melphalan peak concentration in the perfusate, female gender and obesity.[54,55] The higher melphalan uptake in muscle compared to fat is likely the reason why obese patients are more prone to morbidity. The dose of melphalan is based on the volume of the limb. As a result, muscle tissue in obese people is exposed to a relatively higher drug dose.[56] The dose of melphalan is often reduced by 10% in obese patients.[55]

The degree of acute regional toxicity is related to long-term complications.[57] Long-term morbidity is seen in 44% of patients: recurrent infections (3%), neuropathy (4%), chronic pain (8%), muscle atrophy or fibrosis (11%), limb malfunction (15%) or lymphoedema (28%).[57] Lymphoedema can often be attributed to concomitant lymph node dissection, however. Restriction of movement in the ankle joint is reported in 25% of patients.[58-60] Long-term neuropathy is seen in 20% after axillary perfusion and in 2% after perfusion at the iliac level.[61] Complications of the wound do not differ from that seen in other clean operations, whereas vascular complications as bleeding, pseudo-aneurysm, thrombosis and stenosis are rarely seen in experienced centres.

Systemic toxicity of isolated limb perfusion is due to leakage from drugs from the isolated limb to the systemic circulation. The most commonly encountered adverse effects due to leakage from melphalan are nausea, vomiting, leucopenia and thrombopenia, whereas leakage from TNF-α may lead to fever and severe haemodynamic effects, which may be even fatal. Once again it has to be stressed that systemic toxicity can be avoided by adequate isolation of the limb. This can be assured by meticulous ligation of collateral vessels, avoiding a high flow rate, keeping the venous pressure in the limb low and stable, and by continuous monitoring of leakage. In a large series of the Netherlands Cancer Institute, the measured mean cumulative systemic leakage rate was only 0.9 % (range 0-15.6%, standard deviation 2.0%). A thorough wash-out of the limb at the end of the procedure limits the fraction of perfusate that reaches the systemic circulation to a few percent. With these precautions, systemic toxicity is mild or even absent.[62] The perioperative mortality is less than 1%.[62]

Treatment efficacy

Melphalan

The reported complete response rates of isolated limb perfusion with melphalan under mild hyperthermic conditions for in-transit melanoma metastases range from 52% to 82%, while the overall response rates vary from 77% to 100%.[6] The number of lesions and their total surface area are important parameters that predict a response.[63,64] Necrosis of the metastases may become evident overnight but on average it takes three months for a complete response to develop.[44] In some cases it can take up to 9 months for the best response. Approximately 50% of patients with a complete response recur in the perfused limb after a median interval of approximately 12 months following treatment. These recurrences can be managed by simple local treatment modalities such as excision or laser ablation in 70% of the patients. If the recurrent lesions are too large or too numerous, or recur too often, another ('repeat') perfusion with melphalan with or without TNF-α may be considered to stave off amputation (see below).[65] Ten-year survival in patients with initially a complete response is 49%,[44] while long-term survivors have a better quality of life than comparable control individuals.[66]

About 25% of patients develop a partial response after isolated limb perfusion with melphalan.[44] Half of these can also be managed by simple forms of local treatment. With this approach, the limb salvage rate in patients with truly unresectable disease is 96%. Amputation for intractable recurrence is required in 2.4% of the patients.[67]

Melphalan + TNF-α

In series mainly from European centers, the response rates after mild hyperthermic isolated limb perfusion with melphalan and TNF-α were reported to be slightly better than with melphalan only; complete response rates varied from 59% to 90% and overall response rates from 64% to 100%.[6] The median response duration was also longer (8-26 months vs. 6-14 months).[6] In a retrospective comparative study,[68] isolated limb perfusion with melphalan and TNF-α was associated with a higher complete response rate (60% vs. 42%, p=0.036) without a difference in toxicity. In order to get FDA approval, in the U.S.A. a multicenter randomized trial (ACOSOG Z0020) was performed.[69] Patients with unresectable in-transit melanoma metastases were randomized to isolated limb perfusion with melphalan only or to isolated limb perfusion with the combination of melphalan (10 mg/L for the lower limb or 13 mg/L for the upper limb) and TNF-α (3 mg for the lower limb or 4 mg for the upper limb). Since at 3 months after treatment the response rates did not differ (overall response rates 25% and 26%, overall response rates 62% and 69%, respectively) and the severe (grade IV) toxicity was significantly higher in the melphalan + TNF-α group of patients, the study was preliminary closed after inclusion of 133 of the planned 216 patients and FDA approval was not obtained. Notably the response rates were much lower than in other series. Although the study design requested end evaluation of the response after 3 months, a large proportion of the patients was examined 6 months after treatment. After this 6-month interval the complete response rate after isolated limb perfusion with melphalan and TNF-α was much higher than with melphalan only (42% vs. 20%), while a larger number of patients retained their complete response which was observed after 3 months (80% vs. 65%) and a number of patients that had a partial response at 3 months developed eventually a complete response (24% vs. 0%). Thus it seems that after isolated limb perfusion with melphalan and TNF-α the best response is observed later and lasts longer. Moreover, in the final report of this randomized study there was no differentiation in size and number of lesions treated. However, an earlier interim-analysis revealed that in a subgroup of patients with bulky (>5cm) and multiple (>10) lesions the complete response rate on isolated limb perfusion with melphalan and TNF-α was 58%

compared with 19% for melphalan only ($p<0.05$).[31] These observations were recently sustained in an Italian retrospective study showing a 70% complete response rate in a group of patients with bulky melanoma treated with isolated limb perfusion with melphalan and TNF-α.[70] The tumour bulk of the melanoma in-transit metastases can indeed be crucial in appraising the TNF-α effect, as these large, sarcoma-like lesions benefit the most from the destruction of tumour associated vasculature by TNF-α. Therefore, TNF-α might have got FDA approval when the study design had requested response assessment after 6 months and especially for limbs with a higher melanoma tumour load. Based on the presently available evidence, the use of TNF-α in isolated limb perfusion is definitely recommend for bulky disease.[29] Moreover, a lower TNF-α dose (1 mg instead of 3 or 4 mg) appeared to be associated with similar efficacy and locoregional toxicity, carries a smaller risk of systemic toxicity and incurs lower costs.[68,71]

In a recent study,[5] long-term follow-up after isolated limb perfusion with melphalan and TNF-α for in-transit melanoma metastases demonstrated 5- and 10-year disease-specific survival rates of 27.3% and 16.4% respectively; the median disease-specific survival time was 24 months. In multivariable analysis, age, stage of disease and response were strong predictors of survival. Median disease-specific survival after a complete response was 44 months, with a 5-year disease-specific survival rate of 38%. In patients who showed a partial response or no change to isolated limb perfusion with melphalan and TNF-α, median disease-specific survival was 12 months ($p<0.001$).

Repeat isolated limb perfusion

In the case of unresectable limb recurrence after isolated limb perfusion, a second isolated limb perfusion may be considered. Repeating a perfusion at the same level is technically challenging as the vessels are often embedded in rigid fibrosis. A different level is more attractive, for example, femoral instead of iliac. The complete response rate (62%-76%), the limb recurrence-free interval (9-14 months) and the regional toxicity are similar to that of the initial limb perfusion.[65,72-74] Especially in the case of prior isolated limb perfusion with melphalan alone or other drugs, repeat isolated limb perfusion with melphalan and TNF-α seems to be indicated.[75]

Isolated limb perfusion as adjuvant treatment

The favourable results in patients with extensive regional metastases generated the question whether perfusion could also be effective in adjuvant settings. A multicenter randomized clinical trial involving 832 patients examined perfusion as an adjunct after excision of high-risk primary melanomas, defined as a Breslow thickness of at least 1.5 mm.[75] The patients underwent wide local excision of their melanoma and were randomized to adjuvant limb perfusion or observation. Initially, disease-free survival was significantly better for the patients in the perfusion group who did not undergo elective lymph node dissection ($p=0.02$). Later, the survival curves came back together and after two years the disease-free survival was similar in the two groups. The overall survival did not differ. There was a beneficial impact of limb perfusion on the occurrence of in-transit metastases, which was reduced from 6.6% to 3.3% ($p=0.05$). The incidence of lymph node metastases was reduced from 16.7% to 12.6%, but the difference was not statistically significant. Another randomized study examined the value of adjuvant perfusion in 69 patients with resectable recurrent melanoma.[76] After radical excision of their local recurrence, satellites and/or in-transit metastases, patients were subjected to adjuvant isolated limb perfusion or they were observed. Limb perfusion reduced the locoregional recurrence rate non-significantly from 67% to 45% ($p=0.13$). The median disease-free interval was prolonged to 17 months after adjuvant limb perfusion compared to 10 months after excision only ($p=0.04$). The 44% 5-year overall survival in the perfusion group appeared slightly better than the 39% in the observation arm, but

the difference was not statistically significant. The conclusion of these two studies was that isolated limb perfusion is not indicated as adjuvant treatment. Although limb perfusion appeared to have some potential to sterilize tumour cells in lymph vessels and nodes since it postpones recurrence, the costs, morbidity and lack of improvement of overall survival makes it not an attractive adjuvant treatment option.

However, adjuvant perfusion may have a place in patients with multiple and frequently recurring resectable in-transit metastases. The median limb recurrence-free interval in 43 patients, in whom metastases had been excised at least three times, had decreased significantly between time of the primary excision and the third or fourth limb recurrence.[77] Perfusion was performed when the patients recurred once again. Afterwards, the median limb recurrence-free interval was 4.7 times longer than prior to the perfusion ($p<0.001$). The mean number of subsequent lesions was 2.6 fold less compared to before perfusion ($p<0.001$). Perfusion in this study thus lengthened the limb recurrence free interval and decreased the number of recurrences significantly. These results justify the conclusion that perfusion is a valuable intervention in patients with repeatedly recurring in-transit metastases whose recurrence-free interval is steadily decreasing.

Comparison with isolated limb infusion

Isolated limb infusion is a more recent, minimally invasive procedure that was developed as an alternative to isolated limb perfusion. Isolated limb infusion was pioneered at Melanoma Institute Australia.[78,79] Reports from other centers suggest a lower fraction of complete responders compared to isolated limb perfusion,[80-82] but no study to date has directly compared the two procedures. Since the isolation of the limb is not optimal, the administration of TNF-α is not indicated in isolated limb infusion, whereas regional lymph node dissection cannot be concurrently performed. Moreover, the morbidity from isolated limb infusion appears to be somewhat greater, which may be contributed to the less adequate vascular isolation of the limb (systemic toxicity) as well as the hypoxia of the limb in the absence of an oxygenator as in isolated limb perfusion (regional toxicity). Advantages of isolated limb infusion are: it is a less complex and cheaper procedure, requires less advanced technology and is easier to be repeated.

Comparison with novel systemic therapy

Conventional systemic chemotherapy and immunotherapy have not been effective in the treatment of in-transit melanoma metastases. Will perfusion be replaced by systemic therapy with new agents such as like vemurafenib and ipilimumab? The high 54% complete response rate of perfusion and its modest morbidity compare favorably with the 0.9% and 1.6% complete response rate with substantial morbidity of the new drugs.[83,84] At present isolated limb perfusion (and infusion) should remain the first choice for patients with extensive disease limited to a limb. For patients who also have distant metastases, however, systemic therapy with novel drugs may be a more attractive option. Nevertheless, adequate palliation is often achieved by isolated limb perfusion in patients with symptomatic but unresectable locoregional limb involvement. Hence, this procedure should be considered as palliative treatment especially when systemic disease is limited or associated with substantial prognosis, as discussed previously.

Availability of isolated limb perfusion

The relatively low availability of isolated limb perfusion compared to the administration of systemic treatment should not be a reason to preclude this technique. Patients with the above mentioned indications should be referred to centres which have isolated limb perfusion in their therapeutic repertoire. In Greece, unfortunately only one centre (the Department of Surgical Oncology of the Medical School of Crete University Hospital) is performing this treatment modality.

CONCLUSIONS

Isolated regional perfusion is an unusual form of therapy, specifically suitable for the biology of melanoma with its peculiar in-transit dissemination. Perfusion is effective across the entire range of metastases from subclinical disease to bulky lesions. Isolated limb perfusion with melphalan combined or not with TNF-α results in a complete response in 50-90% of the patients with in-transit melanoma metastases. Such a response is durable in half of these individuals. Half of the patients with a complete response survive for ten years, most with an excellent quality of life. In patients who continue to develop in-transit metastases, perfusion can delay and diminish subsequent limb recurrence. Given the complexity of the technique, however, this form of treatment is best restricted to specialized melanoma treatment centres.

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REVIEW

Head and neck reconstruction with the infrahyoid flap in the era of free flaps

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ABSTRACT

Head and neck cancer resection results in local defects with loss of functioning tissue, which can lead to a broad range of functional impairments. The head and neck area is a particularly complex region providing very important functions: respiration, voice production, articulation, and swallowing functions. The choice regarding the type of reconstruction depends on the characteristics of the anticipated defect and on patient's related factors. Differing from the majority of pedicled myocutaneous flaps for head and neck reconstruction, the infrahyoid flap is thin and pliable and this intrinsic characteristic carries an advantage in terms of functional results, making this flap even competing with fasciocutaneous free flaps in the management of medium sized defects of the floor of mouth, alveolar ridge, and base of tongue.

KEY WORDS: head and neck cancer, reconstructive surgery, infrahyoid flap

INTRODUCTION

The management of patients with head and neck cancers is complex, therefore a multidisciplinary approach is frequently needed in order to achieve optimal treatment. Head and neck squamous cell carcinoma (HNSCC) accounts for more than 90% of all head and neck cancers. One third of the head and neck cancer patients presents with early stage disease, while in two-thirds head and neck cancer is diagnosed in an advanced stage. Early stage disease is mostly cured with a single modality treatment, usually surgery or radiotherapy, while more advanced cancers require a combination of surgery, radiotherapy and/or chemotherapy. Several host and tumour factors must be taken into consideration in treatment planning: patient's general conditions (performance status) and specific comorbidities that might prevent withstanding of the treatment, the chances of obtaining a free margin resection in case of surgical intervention, the possibility of delivering curative doses of

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radiation without damaging vital structures, the locoregional volumetric extension of the disease and the presence or absence of distant metastases.

A thoughtful analysis regarding the impact of treatment on quality of life must be taken in consideration since HNSCC proves to be associated with serious deterioration in quality of life; not only tumor-related factors, but also the combined multimodality treatment, including surgery, chemotherapy and radiotherapy, proves to have a profound effect on function and quality of life. Even though these treatments contribute to increased disease control for locally-advanced head and neck cancers, they come at the expense of increased acute and late effects. The three major advancements in the management of HNSCC during the last 30 years are represented by the introduction and the development of non-surgical organ preservation protocols; by the refinements of endoscopic and, more recently, robot assisted minimally invasive surgical techniques; and by the application of microvascular free flaps in head and neck reconstructions.

RECONSTRUCTIVE SURGERY

Head and neck cancer resection results in local defects with loss of functioning tissue, which can lead to a broad range of functional impairments. The head and neck area is a particularly complex region providing very important functions: respiration, voice production, articulation, and swallowing functions. The choice regarding the type of reconstruction depends on the characteristics of the anticipated defect and on patient's related factors: age, performance status, general comorbidities, and previous treatments (especially within the head and neck area).

In head and neck surgery, the type of flap used for reconstruction depends on the needs of the recipient site, in some situations free flaps are required (e.g. in segmental bony reconstructions), whereas pedicled flaps cannot always offer the amount or type of desired tissue, or the defect can result out of reach when the arc of rotation of the vascular pedicle limits the required distance of transfer. However, premorbid patient factors and regional anatomy (e.g. comorbidity or previous head and neck cancer treatment) are also important in deciding which flap is employed for reconstruction.[1]

Free flaps

Randomized controlled trials, comparing microvascular free flaps with regional pedicled flaps in head and neck reconstructions, are not feasible; consequently, the nature of studies comparing these two procedures is restricted to descriptive reports, stratifying, wherever possible, for patient and tumour factors, without the possibility of eliminating inevitable bias. Several authors report that free flaps have advantages over pedicled flaps in head and neck reconstruction, and this is certainly true as respect to the fact that tissue dimensions and thickness can be tailored to the size of the defect and vascularised bone can be used to reconstruct complex defects, all leading to superior restoration of form.[2] Some reports state that free flaps provide superior speech and swallowing outcome over pedicled flaps,[1,3] while other authors were unable to substantiate this finding.[1,4] Many reports regarding the elderly in relation to microvascular free flap reconstruction agree that age is a risk factor for poor surgical outcome;[5-8] older patients prove to be less capable of coping with large fluid shifts and significant blood loss,[5] and free flap reconstructions are known to be more often associated with the need for blood transfusion.[7] In addition, cardiovascular disease proves to be an important factor in free flap reconstructive failure,[5] a condition which is more prevalent in adults past the age of 60 years,[9] furthermore with increasing age there is a greater likelihood of postoperative complications after free flap reconstruction,[10] even with successful microvascular reconstructions.[11] McCrory et al[6] described that operative time, resection-reconstruction, was statistically much longer for free flap than for pedicled flap

procedures (9 hours 35 min versus 4 hours 58 min); long surgical times was a significant factor for the development of postoperative complications in a series of 104 free flaps in patients aged 65 and older.[5]

Besides age, also diabetes appears to interfere with free flap survival,[12] however its impact on healing outcome following microvascular reconstruction is still much debated. While some authors support a negative effect,[13,14] Cooley et al[15] reported that patients with diabetes were not at increased risk either for flap failure or for abnormal healing of the anastomoses as long as normal glycaemia is maintained.

The use of free flaps reconstruction in previously irradiated patients or patients who underwent prior (chemo)radiation is also much debated in literature. In a review, Wong et al[16] pointed out that prior (chemo)radiotherapy can cause significant scarring and vessel damage to the recipient vessels with obvious negative consequences. Furthermore, Schultze Mosgau et al[17] reported a reduced clinical success rate (84%) of free flaps in head and neck patients with previous radiotherapy of 60-70 Gy. Moreover, in a study of 429 patients who underwent free flap reconstruction in the head and neck, preoperative radiotherapy (irrespective of irradiation doses) was significantly associated with fistulae formation and wound infection, while previous neck irradiation at doses of more than 60 Gy proved to be a significant risk factor for free flap failure, overall local complications, hematoma, longer duration of enteral nutrition and hospital stay.[18]

Since intake of alcohol ≥30g/day is related to the development of head and neck cancer,[19] many head and neck cancer patients suffer from alcohol related problems. Both acute alcohol withdrawal as well as other alcohol-induced disorders prove to negatively influence the outcome of microvascular free flap tissue transfers.[20-22]

Consequently, those patients presenting with the above mentioned clinical conditions, which are associated with a higher rate of free flap failure or postoperative complications, are less eligible for microvascular free flap reconstructive surgery, whereas locoregional pedicled flaps may offer a reliable alternative for reconstruction.[23-25] A pedicled flap reconstruction brings some benefits for both patient and surgeon: the surgical procedure is usually less time consuming corresponding with a decrease in the morbidities of prolonged general anaesthesia; most donor sites have low morbidity and usually are amenable to primary closure; the admission length of patients receiving a pedicled flap reconstruction are shorter than those undergoing a free flap reconstruction, with shorter intensive care stay.[6,13]

Consequently, free flap reconstructions can result more expensive than pedicled flap reconstructions [6,26,27] and pedicled flaps, in selected cases, even seem to be preferable over free flaps.[10,27,28] In a matched paired analysis comparing 40 oral cavity/oropharyngeal reconstructions with free radial forearm flap with 40 patients receiving the pectoralis major flap for similar defects, de Bree et al[29] found shorter admission times and lower treatment costs in the free flap group. Nevertheless, the pectoralis major flap can produce some healing delay for frequent necrosis of the most distal edge of the skin paddle; this usually doesn't require further interventions, but it does increase hospital stay and costs. In fact, where conservative transmandibular approaches are employed, the bulkiness of the pectoralis major flap produces less than ideal functional outcomes, because the mandible presses upon the flap favoring hypovascularization and necrosis of the distal portion, and because the thickness and bulkiness of the flap hinders the motility of the preserved structures.

The infrahyoid flap

Differing from the majority of pedicled myocutaneous flaps for head and neck reconstruction, the infrahyoid flap is thin and pliable and this intrinsic characteristic carries an advantage in terms of functional results, making this flap even competing with fasciocutaneous free flaps in the

management of medium sized defects of the floor of mouth, alveolar ridge, and base of tongue. For these sites the infrahyoid flap produces particularly high-quality functional results, the pliable skin paddle is placed and sutured all around the mucosal defect allowing a good mobility of the surrounding structures, and the infrahyoid muscles fill the deep tissue loss coming from resections carried en block with neck dissection, restoring a separation between different compartments created by tumour resection. In case of marginal mandibulectomy, the flap's muscles cover the denuded mandibular bony surface; moreover, the oval/rectangular shape of the infrahyoid flap perfectly matches the usual shape of the resections in these cases. Excellent functional results are also obtained for base of tongue reconstructions,[30,31] especially if the flap is not detached from the hyoid bone, using the reported personal technique.[13]

The infrahyoid flap is a quick, easy, and reliable reconstructive method, when specific contraindications are respected and when used with knowledge of its clinical utility and limitations, the functional results are excellent with great patient's satisfaction; therefore, this overlooked reconstructive method should enter in the toolbox of the modern head and neck surgeon.

The infrahyoid flap is a myocutaneous pedicled flap mainly nourished by the superior thyroid vessels through the perforators of the infrahyoid muscles. This thin and pliable flap provides a skin island of about 7 by 4 cm from the central part of the anterior neck. The flap can be transferred on its pedicle of superior thyroid artery and vein to reconstruct medium sized head and neck defects created after cancer ablation. The infrahyoid muscles included in this flap are the sternohyoid muscle, the superior belly of the omohyoid muscle and the sternothyroid muscle. Usually the flap is unilateral and the side is determined by the location of the defect, therefore the skin paddle and cervical incision for neck dissection are outlined in the same neck side of the tumour resection. The shape of the flap is rectangular or oval in a vertical position, and the skin paddle must be fitted and included in the incision for unilateral or bilateral neck dissection. The technique of harvesting this flap has been described more in detail by Dolivet et al[32] and Deganello et al.[33-35] In a comprehensive review of the available literature reporting on the infrahyoid flap the 7 larger series (cohort larger than 50 cases),[34] a total of 956 flaps were performed, and the global success rate was 91.7%, with failures being mainly related to partial skin necrosis, as the rate of total (skin and muscle) flap necrosis was only 1%.

The advantages of the infrahyoid flap may be summarized as:[36]

- excellent reliability, and low complication rate;
- the donor site is near the defect, allowing the paddle to be easily transferred without torsion or tension of the pedicle;
- minimal donor site morbidity as the cervical donor site is usually primarily closed;
- high pliability, the paddle is thin and flexible not impairing the movements of the preserved oral-oropharyngeal structures, and when the ansa cervicalis is intentionally not included in the pedicle its pliability will increase overtime as direct consequence of the atrophy of the muscular portion of the flap;
- the inclusion of the ansa cervicalis in the pedicle, which prevents atrophy of the muscular portion of the flap, guarantees a consistent neo-tongue bulk overtime in case of oral/ base of tongue reconstruction;
- the paddle allows good coverage of the defect without excessive volume;
- the flap is quickly harvested during the neck dissection by the same surgical team;
- postoperative immobilization of the patient is not required;
- the flap dissection does not require microsurgical expertise and vigilant monitoring; as free flaps do.

Disadvantages of the infrahyoid flap mainly coincide with its contraindications: previous thyroid surgery or neck dissection, N3 neck metastasis,

and positive lymph nodes at level III–IV. All these contraindications pose consistent limitations to the use of this reconstructive option. The infrahyoid flap must always be planned in advance and cannot represent a back-up solution in case of other flap failure, since it cannot be used in a previously operated neck. In fact, probable damages to the superior thyroid artery and/or vein and/or possible elevation of the skin overlying the strap muscles prevent the possibility to rely on this myocutaneous flap.

FUTURE PERSPECTIVES

Nowadays surgical techniques are evolving towards the maximization of the possibility to obtain adequate tumor resection through the natural cavities, avoiding the surgical division of healthy structures in order to gain appropriate exposure.[37-39] This entails the development of sophisticated surgical tools at the service of a simple philosophy: the possibility to obtain a sound oncologic resection through natural cavities. Since oral cancer is already mostly addressed transorally, this shift will particularly impact the surgical treatment of pharyngeal cancer. Surgical cancer resection therefore is becoming less and less invasive with proportional fewer demands for reconstruction. In fact, one of the major indications for reconstructive surgery in the head and neck district is the need of restoring a separation between different compartments that were put in communication to facilitate tumor resection. This specific indication vanishes or is highly restrained when advanced endoscopic or robotic resections are applied through the upper aerodigestive natural cavities, because in most of these cases healing for secondary intention can effectively resurface the defect without the need of transposing a flap. Therefore, the shift of ablative head and neck surgery away from aggressive demolitions in favour of minimally invasive approaches will probably reshape also the indications for reconstructive surgery.

In general, transoral robotic resection applies for small/medium sized oropharyngeal cancers, the resulting defect is usually left to heal by secondary intention, nevertheless it is well known that postoperative bleeding is a recognized threatening complication of transoral robotic procedures.[40] The degree of vascularity can vary significantly among patients as well as the proximity of the tumour to larger vessels supplying the oropharynx. In this light an easily harvestable flap, brought to fill the defect with the aim of protecting major vessels from the erosive action of the saliva, could play an important role enhancing safe healing and preventing excessive scar tissue formation. This opens a perspective for the diffusion of the infrahyoid flap in combination with transoral robotic surgery.

Recently Perrenot et al[41] published a series of 8 patients who underwent transoral robotic surgery for oropharyngeal squamous cell carcinomas associated with immediate reconstruction using the infrahyoid myocutaneous flap. After tumour resection and neck dissection the flap was harvested and transposed into the oropharynx in a minimally invasive way and sutured either completely or partially with the robotic instrumentation. Currently head and neck reconstruction is mostly performed using flaps, in the near future bioengineered materials will certainly play an important role in surgery.[42]

One of the most exciting areas of surgical nanotechnology is that of nerve repair, reconnecting nerves can be extremely difficult; primary repair of severed axons has not been successful traditionally due to practical difficulties of operating on a subcellular level. Surgical tumour resection removes voluntary dynamic and sensate structures, which are replaced by static flaps impairing the possibility of restoring a full functional integrity. Nanomaterials showed a potential ability to guide organization and formation of new tissues for reinnervation on a nanoscale, serving as a temporary scaffold mimicking cellular characteristics to promote axon repair.[43]

Nanotechnology will undoubtedly lead to advancements in the art and science of head and neck reconstructive surgery, and the availability of bioengineered tissues might render the harvest of an autologous free flap something that belongs to the past, in favour of patient compatible tissues, even vascularised, created in the laboratory. The future is exciting, although much research is, however, needed to fine-tune and perfect these materials to tailor them to clinical needs.

The constant human progress and technical evolution will open new perspectives for cancer treatment and surgical oncology. It will be our duty to walk the path of progress with enthusiasm but without completely leaving behind useful tools that belong to the past, but that in the future could still represent a valid option in selected cases. And this is probably the point where the infrahyoid flap stands today in the modern free flap era.

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REVIEW

Perineal reconstruction following extralevator abdominoperineal excision for low rectal cancer

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ABSTRACT

Extralevator abdominoperineal excision of the anorectum (ELAPE) for low rectal cancer is related to a lower incidence of circumferential resection margin compared to the traditional technique. However, there is lack of consensus regarding the optimal technique of reconstruction of the larger perineal defect produced. This review, presents data on the main techniques so far employed in post ELAPE perineal closure, namely primary closure, biological mesh, synthetic mesh, omentoplasty and myocutaneous flaps. Although interesting information considering the features of each technique can be found in the literature, lack of high quality studies renders definite conclusion drawing difficult. Large, prospective randomized trials are warranted to clarify the ideal technique for perineal wound reconstruction.

KEY WORDS: rectal cancer, extralevator excision, abdominoperineal excision, perineal wound, reconstruction

INTRODUCTION

The inconsistency in the oncological results between low anterior resection and abdominoperineal excision (APR) for low-lying rectal cancer, has been attributed to the anatomical characteristics of the latter, which entails adherence to the plain of the mesorectum.[1] This results in a notable "waist" in the specimen, which inevitably reflects higher intra-operative rates and a positive circumferential resection margin (CRM), the latter reaching rates as high as 40%.[2] The above issues have been successfully addressed with the implementation of extralevator abdominoperineal excision of the anorectum (ELAPE), which shifts the level of dissection laterally, to include the levator ani.[3] Pathologic features are in accordance with the surgical technique, since the specimen is cylindrical at the level of the levator, with no "waist", while tissue morphometry proves the resection of more tissue peritumorally, reflecting lower intraoperative perforation rates and positive CRM (<21%).[4,5] The perineal dissection can be performed either in the prone position, which involves intraoperative turning of the patient, or in the traditional supine position.[5,6] Although ELAPE is deemed superior

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anatomically compared with the standard APR, it is associated with a significantly larger perineal defect, and potentially with higher rates of perineal hernia, a well known complication of standard APR,[7] observed in as many as 7% of cases.[1] While a variety of techniques has been employed to repair perineal hernia,[1] it seems reasonable that prophylaxis suggests the best strategy.[8] Various techniques have been proposed and published for closure of the perineal defect. Apart from the technical challenges of some of these, poor wound healing is the common denominator in these high-risk patients who have undergone neoadjuvant pelvic radiotherapy, and should always be borne in mind.[9] The scope of this review is to present the various techniques employed for perineal reconstruction after ELAPE, and briefly present the outcome from their implementation.

TECHNIQUES

Primary Closure

Primary closure entails elimination of the perineal defect via simple approximation of subcutaneous tissue. The obvious advantage is the minimal burden concerning operative time, while the usage of irradiated tissues in the absence of muscular support, suggests the technique's Achille's heel. In a multicenter study, West et al made a comparison between a group of 176 patients who underwent ELAPE and 124 patients who underwent traditional APR excision, considering the patients' outcome.[4] In 50.6% of patients of the ELAPE group, perineal reconstruction was performed using a muscular flap, porcine collagen mesh (Permacol) was utilized in another 6.25%, while in 43% of patients, the perineal wound was closed primarily. No difference in outcome was observed between primary closure and perineal reconstruction. The outcome of abdominosacral rectal amputation over a 10-year period (n=210), was described in a large non-multicenter study.[10] In this study, primary closure and perineal drainage was used, while the pelvic cavity was obliterated with gauze packing for up to 12 days.[10] Both major wound complications, as well as perineal hernia rates, stood low, at 5.76%.[10] Primary perineal closure was also evaluated in a large case series (n=160), where an increased rate of serious complications (35%) was evident, particularly delayed wound healing and infection.[11] These high rates have been, at least in part, attributed to the significantly higher rate of neoadjuvant chemo radiotherapy compared to the previous one (73% vs 20%). Finally, De Campos et al[12] observed extremely low wound complication rates (10-14%), and 0% of perineal hernias, in a study utilizing primary repair of the perineal defect (n=168). Collectively, while the actual frequency of perineal hernia formation after ELAPE is largely unknown, it seems reasonable that unless the pelvic floor is reinforced, the risk of perineal hernia is potentially significant, and this suggests the main reason for the employment of various techniques for reconstruction of the perineum.[1]

Biological mesh

These implants, suggest acellular biological structures made of porcine dermis, human dermis and intestinal submucosa. Since they have been previously employed in the reconstruction of pelvic and abdominal wall defects,[13] there was a thought of using them for perineal hernia repair and perineal reconstruction after ELAPE.

This type of mesh is estimated to promote neovascularization, tissue remodeling and cell ingrowth, while their biocompatibility compared with traditional synthetic mesh is extraordinary, since the former can be successfully used even in contaminated operations.[14] Obvious benefits over the employment of myocutaneous flaps are reduced operative time and the lack of necessity of involvement of plastic surgeons in the operation, while potential morbidity by the use of myocutaneous flaps, such as delayed post-operative ambulation, flap necrosis, as well as complications from the donor site, imply that biomesh employment may potentially prove more cost-effective.[15]

In a large study performed by Christensen et

al[16] biological mesh (n=24) was compared to closure with gluteal flaps (n=33) and revealed higher incidence of wound infection in the group where permacol biomesh was used (21% vs 9%). On the contrary, perineal herniation was noticed in the group of gluteal flaps (21%), but none in the permacol group. Two studies, Han et al (n=12) and Jorgensen et al (n=11),[14,17] observing patients for 8-12 months, where biological mesh was used, reported no incidence of perineal herniation. However, high rates of perineal pain were reported (48%), exceeding even those reported in ventral hernia repair with synthetic mesh (28%).[14] The pain however diminished within 2 months in most of the patients, apart from one case where the pain lasted for 26 weeks, mimicking the chronicity of symptoms associated with synthetic mesh repair. A plausible explanation for persistent perineal pain is coccyx excision. In 15 cases where Permacol mesh was employed, Noble et al[18] reported high rates of perineal sinuses and delayed wound healing (20-48%), slightly correlated with the female gender.

In a pooled analysis performed by Butt et al[1] comprising 149 patients who underwent ELAPE, 68.5% of whom had undergone neoadjuvant chemoradiotherapy, perineal closure was evaluated using Permacol (n=101), surgiSIS (n=19), human acellular dermal matrix (n=12) and cross-linked acellular porcine dermal collagen (n=17). During short- to medium-term follow-up, 20 (13.4%) major wound complications, 41 (27.5%) minor wound complications, as well as 4 (2.7%) perineal hernias. Of note are 2 cases of small bowel obstruction associated with the use of Permacol mesh.[19] Both patients had T4 tumors and had received neoadjuvant chemoradiotherapy, while adhesions between the bowel and the mesh, was the cause of obstruction. This has put questions over the widespread use of biomesh, warranting the performance of further assessment, before liberally advising for its general use.

Synthetic mesh

The contaminated surgical field of the perineal wound post-ELAPE, accounts for the scarcity of studies employing synthetic mesh for perineal reconstruction. One small ELAPE case series utilized a Vicryl mesh tension-free technique for closure of the pelvic floor (n=4). In one of the patients, small bowel obstruction was observed, although it was said to be irrelevant to the technique.[20] More ELAPE studies are definitely warranted.

Omentoplasty

Omentoplasty is a method used for more than 30 years -often combined with primary closure- in order to restore the pelvic floor after ELAPE. Thanks to its rich lympho-vascular supply, omental flaps can easily be transpositioned to the "dead space" that is created after the excision of the rectum together with the perirectal fatty tissue. The chief advantage of omentoplasty is the use of an autologus material with a significant immune action. Furthermore, it reduces the incidents of surgical wound infection, prevents fluid collection and creates a relatively strong "pelvic ground" which averts the creation of hernias or adhesions between small bowel loops and the presacral area, therefore protecting patients from future small bowel obstruction.[21] Essential prerequisites are the presence of healthy tissue and an adequate length, with sufficient blood supply of the mobilized omental flaps. Ten observational studies of omentoplasty from 1970 to 2005 indicate only a few complications including bleeding, necrosis or internal herniation (n=4/366) and minor infective complications in 4-28%.[22] The rates of successful primary healing in a time interval of 3 months were up to 87-100%, but the studies did not provide enough evidence-based benefits compared to the primary closure alone.

Hultman et al[21] compared the results of perineal wound healing in APR, with and without omentoplasty over a time period of 9 years. Isolated primary closure of the pelvic floor (n=13) or muscular flap (n=28) alone demonstrated significantly higher rates of both minor and major complications, such as formation of a pelvic

abscess, bowel obstruction, flap necrosis and dehiscence, creation of an urinoma or even deep vein thrombosis, compared with omentoplasty, either alone, or combined with a muscular flap (n=29).

Interestingly, in a recent retrospective case series with a median follow-up of 17 months performed by Saklani et al[23] combined omentopexy and either biological mesh or a myocutaneous flap, was superior to omentoplasty alone, regarding perineal herniation.

It should be borne in mind that omentoplasty might be contraindicated in a significant number of cases, for instance in patients with metastatic involvement, previous omentectomy, former abdominal surgeries or inflammatory procedures which potentially prohibit omental mobilization, reduce its malleability. Suffice it to say, that during laparoscopic abdominal surgery, it is not always possible for the created omental flap, to reach the pelvis.[1] It also seems that omentoplasty is a beneficial technique to restore the perineal wound after ELAPE, when combined with primary closure, biological mesh or a myocutaneous flap rather than by employing it as a sole technique.

Perineal closure with myocutaneous flaps

The main rationale for the use of myocutaneous flaps in perineal reconstruction during ELAPE, is the enhanced healing process by the provision of better perfusion, oxygenation and leukocyte concentration, all of which are of primary importance in the presence of an irradiated surgical field. As expected, optimal results regarding the incidence of perineal abscess formation, major wound dehiscence and drainage of pelvic fluid collections, have been reported by the utilization of rectus abdominis myocutaneous flaps, compared to primary closure alone.[24]

Gluteal flaps

A study, originally from Holm et al[3] followed the cases of 28 successive patients, in which a gluteus maximus flap was used for perineal closure after prone ELAPE. Of these patients, 23 were treated with neoadjuvant radiatiotherapy and had a follow-up of between 1 and 45 months. The outcome included 3 wound infections as well as 4 complications associated with the flaps. Recommendation of the authors for the use of gluteal flaps lies in the fact that the rate of wound complications is low and because of the adjacent anatomy, closure is done without tension and with all skin layers in use in contrary to primary closure, in which only skin and fat participate. A variety of extent of gluteal muscle was spared, ranging from half to two thirds. According to the patients, no significant functional reduction was present. A comparison of these results was made with these of Haapamäki et al[25] which involved physical function and quality of life after ELAPE (n=19). This cohort study presented impaired ipsilateral flexion strength, balance and pain during sitting compared to a matched reference population during a mean follow-up of 26 months. An increased number of wound complications were also reported such as delayed healing (5/19) and deep wound infection (5/19). In another study, Anderin et al[26] showed that the unilateral gluteus maximus flap for ELAPE reached an encouraging 91% rate of complete healing at 1 year, but on the other hand, was associated with early wound complications of the perineum (41.5%) that required intervention, such as wound dehiscence and pelvic abscesses. Boccola et al[27] analysed the inferior gluteal artery myocutaneous transposition flap (IGAM) in ELAPE and its outcomes, relatively to rotational gluteal flaps (n=8). Of these cases, only one wound breakdown occurred superficially and successfully resolved conservatively within 3 weeks. Median follow-up was 11 months. Among the last study's report, it is mentioned that hip flexion strength and gait were preserved, in contrast to previous studies, and the authors suggest the attribution of sparing most of the gluteal muscle, a 'split muscle' technique. A series of prone abdominoperineal resection with gluteal flap closure was done by Mathias et al[28] over a 3-year period up to 2006 and 13 out of 16 patients received neoadjuvant

radiotherapy. Development of perineal wound infections was reported in seven patients but no further information was disclosed considering flap-related complications or primary wound healing.

Rectus abdominis and gracilis flaps

The study of Chan et al[29] compared the outcomes of primary perineal closure (n=21) with a vertical rectus abdominis myocutaneous flap (VRAM, n=24) or a gracilis flap (n=6). The group of myocutaneous flaps developed complications such as herniation of the donor site, a late incisional hernia, as well as flap-associated complications necessitating reoperation in 5 cases. Regarding the primary repair group, 4 cases of wound breakdown, 3 of which required debridement and VAC/maggot therapy and 1 requiring pelvic abscess drainage were observed.

Petrie et al[30] described the outcomes of 18 patients who underwent perineal reconstruction with myocutaneous flaps. Six of those had undergone ELAPE, where 5 VRAM flaps and 1 free latissimus dorsi flap, had been utilized. Although minor complications such as a case of superficial epidermolysis and 3 cases of flap edge dehiscence were noted, no discharge delay was observed. The authors however did not specify the time points of the primary repair, so as to measure the outcome.

Nisar et al in a prospective study including 13 patients undergoing ELAPE where a VRAM flap was employed,[31] was more specific in the provision of data regarding perineal wound healing rates. More specifically, 6 patients achieved uneventful recovery between 21 and 90 days (median, 42). Seven patients though, had delayed wound healing attributed to minor perineal breakdown (median, 69 days), with 2 of them requiring the application of VAC (mean, 120 days).

Finally, McMenamin et al[32] applied a VRAM flap in the reconstruction of perineal wound of 16 patients, with 50% suffering perineal wound breakdown, 1 flap failure and 3, donor site herniation. The use of interrupted nylon sutures over subcuticular monofilament suture was also recommended, so as to avoid wound dehiscence.

DISCUSSION

Complications associated with the perineal wound, suggest a traditional issue in APR, and are anticipated in ELAPE, since the latter is consistently gaining global popularity. The potentially superior oncological features of the technique should not be at the expense of patients 'morbidity. The introduction of all of the above mentioned techniques for perineal reconstruction is based on the logical assumption that the larger perineal wound defect produced during ELAPE, unless reconstructed, will result in herniation. Unfortunately, there is lack of long-term observational studies of ELAPE and primary closure.

Primary closure does not address the defect of the pelvic floor, and in case of administration of neoadjuvant chemoradiotherapy, wound closure is subject to the impaired healing capacity of previously irradiated tissues.[1] The employment of omentum seems a rather appealing solution, but its availability is inconsistent, rendering the technique ancillary to other employed methods. Apart from that, filling the entire pelvis with omentum might prove a rather demanding task.

Usage of a myocutaneous flap has the unique advantage of offering an irradiation naïve tissue complex, to close the perineal defect. However, the use of a VRAM flap seems inappropriate, especially in cases of laparoscopic ELAPE, due to the insertion of trocars in the anterolateral abdominal wall, and secondarily, due to the increased risk for donor-site herniation. The gluteal flap seems more attractive, but it has to be borne in mind that the operation is significantly prolonged; the presence of a plastic surgeon is warranted and the functional outcomes are far from ideal.

The biological mesh, seems to suggest the most effective answer, as it adds very little to the operation time, avoids the occurrence of donor-site hernia, while it can be placed either in the supine or prone position.[1] Regarding its cost-effectiveness,

it has been reported to be much more convenient, compared with flap employment.[15]

It has to be mentioned that for the time being, the optimal technique for perineal closure post ELAPE, has not been elucidated. Although a higher number of studies making use of biological mesh have been recently published,[1] revealing increased interest in the employment of this procedure, based on the above mentioned advantages of biomesh, no definite superiority of biomesh can be proved. In fact, the outcomes of biomesh use are comparable to those of primary closure, omentoplasty and myocutaneous flap use.[1]

Since most of the above presented data are qualitative, it is not easy to draw conclusions considering the optimal technique for perineal closure, as ELAPE itself was only recently introduced and the cohorts involved in the studies are small.[1] Furthermore, absence of control subjects and well-defined outcome measures, render comparison of the outcomes of the techniques challenging.[1] A primary endpoint regarding perineal wound healing may make technique comparison feasible, since a long-term follow-up would thus be obviated. Perineal wound healing and appropriate time points could be clarified using the ASEPSIS scoring system which refers to a means of surgical site infection evaluation, as well as the Southampton Scale, which categorizes wound complications with grading from o to V, also incorporating wound management post-discharge.[33]

In conclusion, a large number of prospective studies, mainly randomized controlled trials utilizing cohorts matched for various parameters including neoadjuvant chemoradiotherapy among others, comparing the various closure techniques, are warranted. A cost analysis, would also aid the determination of the most convenient and effective closure method. This information will certainly help in the decision-making of perineal wound closure to eliminate complications and avoid prolonged hospitalization and potential reoperation.

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CASE REPORT

Breast metastases from ovarian cancer

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ABSTRACT

Ovarian carcinoma is a highly prevalent disease worldwide with most cases metastasizing into the abdominal cavity. Metastatic ovarian carcinoma to the breast is a rare entity and can mimic primary breast carcinoma. In this article, we present a 45-year old woman with a history of ovarian cancer who presented with a unilateral breast enlargement and found to have biopsy proven ovarian cancer metastases in the breast tissue. Despite the high incidence and prevalence of primary breast cancer, metastasis from extramammary origin should be suspected in patients with a prior history of another malignancy. Its recognition is important because the prognosis and treatment differ greatly from that of primary breast cancer. Given the poor prognosis of metastatic disease, the treatment should be individualized. Wide local excision of the tumour or mastectomy may be considered in patients with metastatic disease limited to the breast, or with minimal disease burden elsewhere.

KEY WORDS: breast metastasis, ovarian cancer

INTRODUCTION

While primary breast carcinoma is the most common malignancy in women, metastasis to the breast from extramammary malignancies is rarely seen in clinical practice. Metastases to the breast are rare and account for approximately 2% of all mammary malignancies.[1,2] The most common metastatic lesion to involve the breast is a metastasis from a contralateral mammary cancer.[1,2] If haematological malignancies are also excluded, the number of metastases to the breast from extramammary origin drops to well below 1%.[1,3] They usually develop in the fifth or sixth decade and the patients most often have prior history of a malignant tumour with documented metastatic spread.[1,2,4–6] A wide variety of malignancies that metastasize to the breast has been reported. Owing to the frequency of primary breast cancers and the rarity of non-mammary tumours involving the breast, a newly discovered lesion in the breast is usually presumed to be a primary breast carci-

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noma. However, the recognition of non-mammary metastases to the breast is very important, as both the treatment and prognosis differ significantly. Establishing the correct diagnosis is crucial so as to avoid unnecessary surgical procedures and inadequate treatments in these patients.

Herein, the case of a 44-year old woman with unilateral breast enlargement due to metastases from ovarian cancer is discussed and the literature is reviewed.

CASE REPORT

A 45-year old female with a history of ovarian cancer presented with unilateral breast enlargement. She was diagnosed with ovarian cancer and peritoneal carcinomatosis 17 months before. Initially she underwent complete cytoreductive surgery, including total hysterectomy with bilateral salpingo-ovariectomy en block with resection of pelvic peritoneum and the rectosigmoid, pelvic lymphadenectomy, omentectomy, appendectomy and resection of the peritoneum and a small full thickness part of the right hemidiaphragm. At the end of the procedure there was no macroscopic disease in the abdominal cavity. Cytology of ascitic fluid was positive for ovarian cancer cells. Histological examination demonstrated bilateral high-grade ovarian serous cystadenocarcinoma with infiltration of the uterus, the vagina and rectum and metastatic disease in the iliacal and perirectal lymph nodes and at the right diaphragm. The omentum and the appendix were free of disease. Subsequently she received seven cycles of paclitaxel, carboplatin and bevacizumab. During and after this systemic treatment she remained in good general condition. At 8 months after the initial diagnosis computed tomography and positron emission tomography were without evidence of disease and the value of tumour marker Ca-125 remained normal. Subsequently she was started on maintenance treatment with bevacizumab. Eleven months after the initial diagnosis the tumour marker Ca-125 started rising without signs of disease recurrence at computed tomography. However, 3 months later she presented with bowel obstruction. At laparotomy strong adhesions of small bowel loops with the left posterolateral abdominal wall and the left ureter were observed. Resection of the involved small bowel with end-to-end anastomosis and resection of a part of the left ureter and creation of a nephrostomy were performed. Histological examination demonstrated infiltration of ovarian cancer recurrence into the small bowel wall and peritoneum. After postoperative recovery she developed dyspnoea due to pleural effusion of the right hemithorax for which repeated drainage was performed. Cytological examination of the pleural fluid remained negative for ovarian cancer cells.

While the pleural fluid production gradually decreased, 17 months after the initial diagnosis of ovarian cancer she presented with enlargement of her right breast. At clinical examination some lumps were palpated in the diffusely enlarged oedematous right breast, while axillary lymphadenopathy was absent. Mammography one month earlier had not shown any abnormal findings. At ultrasound of the right breast derangement of the mammary architecture and some well circumscribed hypoechoic lesions and internal vascularity were observed (Figure 1). Ultrasound-guided core needle biopsy of one of the lesions revealed the diagnosis of breast metastasis from ovarian cancer. Histological examination demonstrated poorly differentiated adenocarcinoma cells, staining positive for Wilms' tumour protein (WT-1) and oestrogen receptor, focally positive for CD56 and progesterone receptor, and negative for p53 and HER2/neu, while the ki-67 index was 60% (Figure 2). Magnetic resonance imaging of the breasts, performed for mapping of the metastases to assess response to systemic chemotherapy, demonstrated diffuse intense contrast enhancement of the enlarged right breast (non-mass lesion) as well as two circumscribed tumours, 1.7 cm and 1.5 cm in diameter, with contrast enhancement in the chest wall at the level of the upper inner

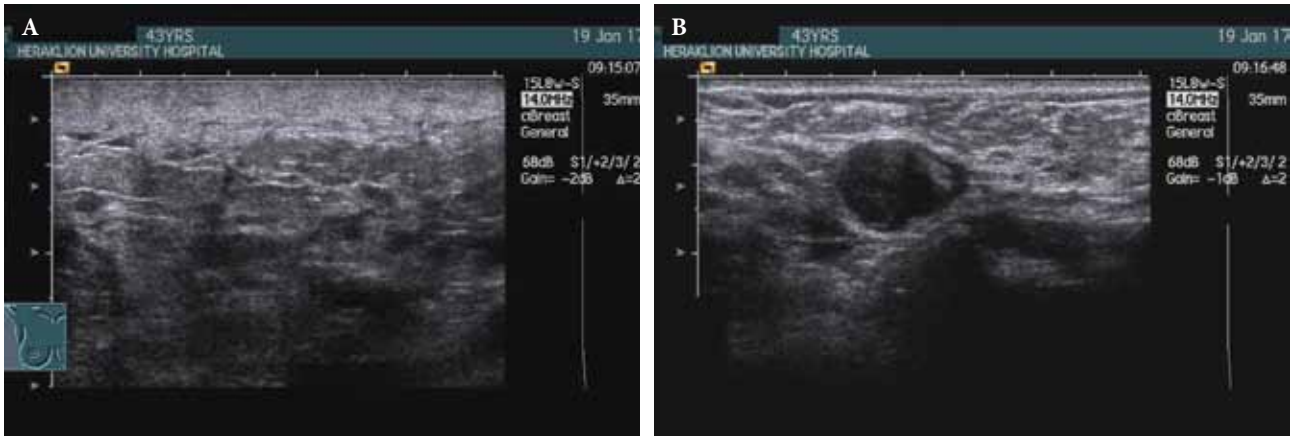

Figure 1. Ultrasound of the right breast demonstrated derangement of the breast's architecture (A) and well circumscribed hypoechoic lesions (B).

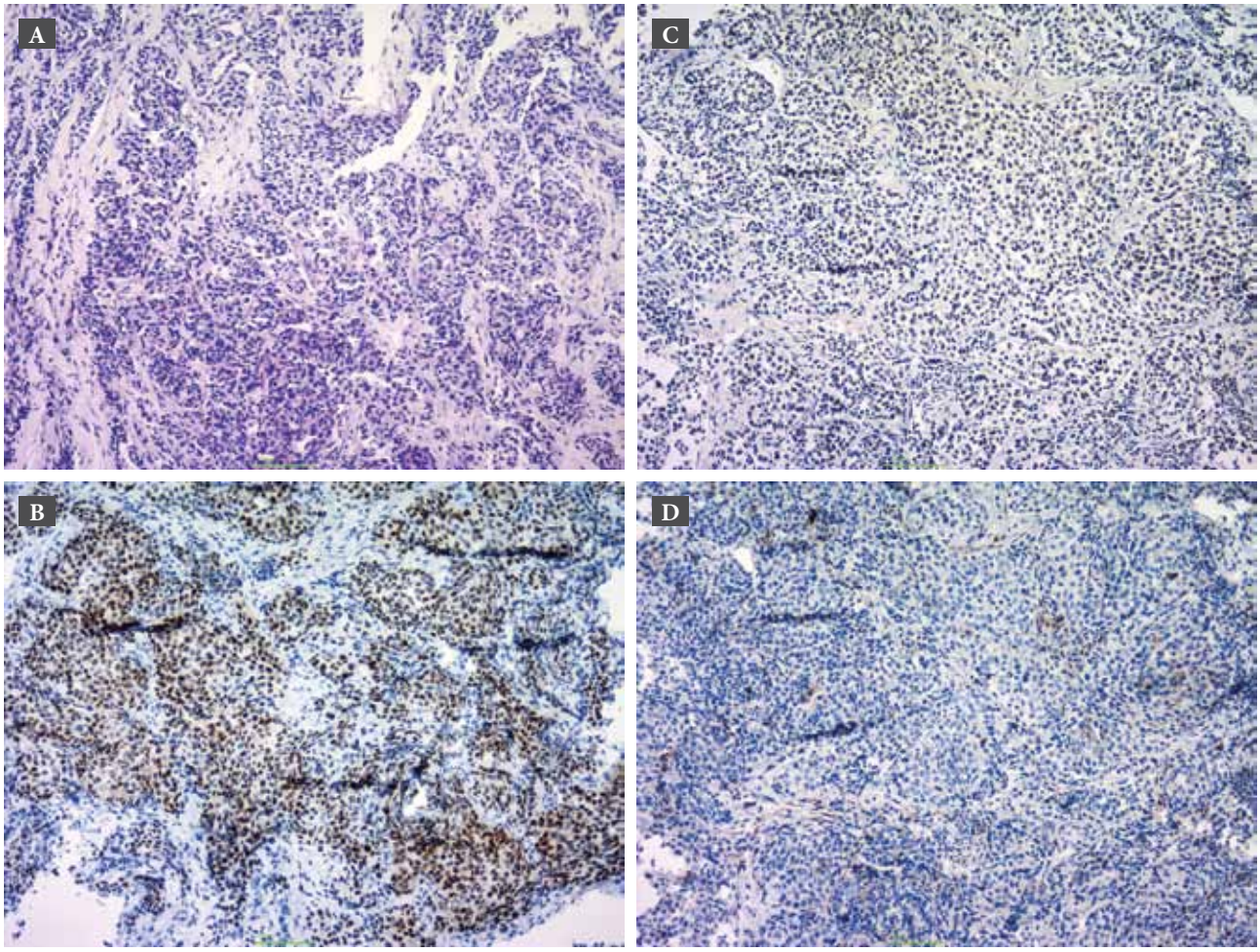

Figure 2. Infiltration of the breast tissue by a low differentiated adenocarcinoma (A, hematoxylin-eosin stain obj. x10), which in immunohistochemical evaluation showed diffuse nuclear positivity to oestrogen receptor (B) and WT-1 (Wilms' tumour protein, C), and focally cytoplasmic positivity to CD56 (D).

quadrant of the right breast and a similar lesion of 3 cm in the lower outer quadrant of the same breast (Figure 3). Enlarged axillary lymph nodes were not observed. Five months after the start of systemic chemotherapy with gemcitabine and carboplatin she remains in good general condition with stable disease in the right breast and absence of clear evidence of recurrent disease elsewhere. When the recurrent disease remains limited to the right breast and the underlying chest wall, performance of radical mastectomy will be considered.

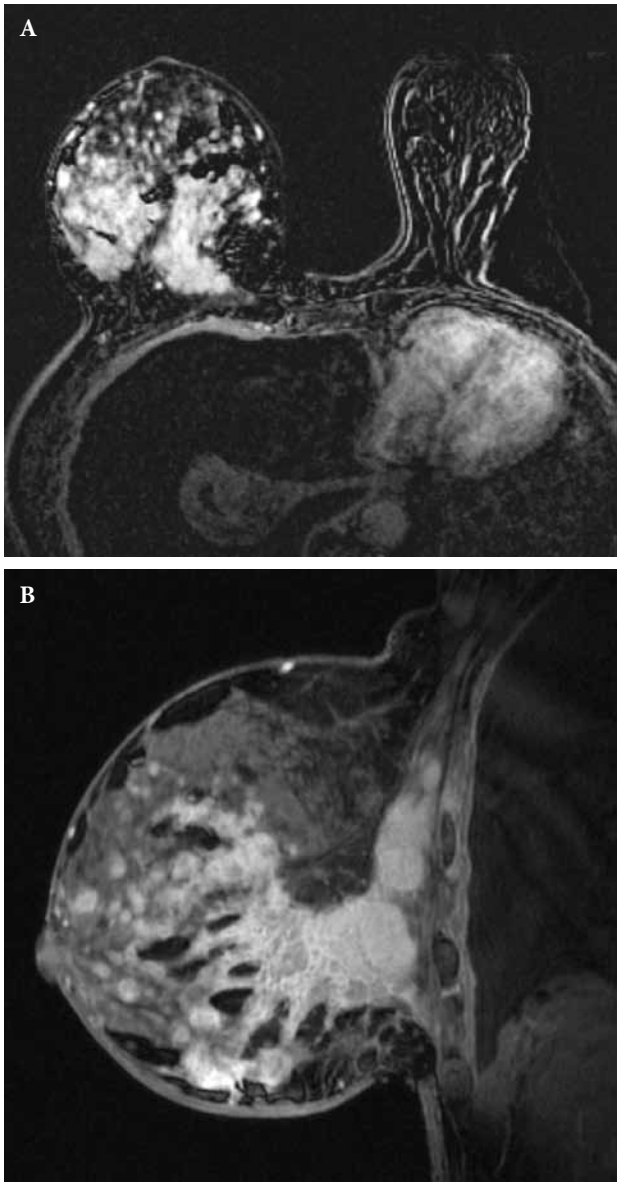

Figure 3. Magnetic resonance imaging of the breast. A: Transversal T1 image demonstrated diffuse intense enhancement of the enlarged right breast, especially at its lower and anterior part. B: Sagital T1 image demonstrated also delayed enhancement of circumscribed tumors in the right breast and major pectoral muscle.

DISCUSSION

Non-haematological metastases to the breast are rare occurrences. A wide variety of malignancies from many different sites have been reported. In a collective review of 24 articles presenting data from 1855 to 1998,[7] a total of 431 cases of tumour metastasis to the breast were identified. The primary sites for metastasis were malignant melanoma (20%), lung (18%), ovary (12%), prostate (9%), kidney (6%), stomach (3%), ileum (3%), thyroid (3%), cervix (3%), and other (23%). In a series of 169 patients diagnosed in a 15-year period at the M.D. Anderson Cancer Center,[6] the most common primary histology was melanoma (39%), while in less than 5% of the cases the breast metastasis was from ovarian cancer. Recently in a retrospective series of the Memorial Sloan Kettering Cancer Center,[8] sarcoma (21%), melanoma (21%), ovarian cancer (16%) and lung cancer (13%) were the most frequent tumour types in 85 patients with breast metastases diagnosed in a 20-year period. Both M. D. Anderson Cancer Center and Memorial Sloan-Kettering Cancer Center benefit from referral bias, which results in these institutions seeing a higher number of unusual manifestations of cancer than other institutions. Furthermore, both institutions aggressively follow patients who have been diagnosed with other primary tumours, resulting in a higher likelihood of detecting these metastases. Nonetheless, the reported series may underestimate overall experience of these centers, because patients with haematological malignancies as well as those with clinically evident, but not histologically confirmed, breast metastases were excluded.

In the above series,[7,8] the median age of those patients was 51-54 years, while the vast majority

of them was female (85-92%). The haematologically disseminated metastases often develop as a circumscribed mass, whereas lymphatic dissemination often presents as diffuse breast oedema and skin thickening. In most of the cases, the breast metastases were unilateral (85-88%) and solitary (75%).[7,8] The patients most often (54-77%) had other metastases at the time of diagnosis of the breast involvement.[7,8] Most patients had a history of malignant disease. However, approximately 10% of the patients had no history of malignancy and the breast metastasis was the first finding that led to the diagnosis of the occult malignant disease.[7,8] A case has been reported in which a breast metastasis of initially unknown origin preceded the final diagnosis of primary ovarian cancer by several years.[9]

In a retrospective study,[10] only 18 cases of ovarian cancer that metastasized to the breast were identified during a 14-year period at the M.D. Anderson Cancer Center. The median age of the patients was 55 years, while the majority of patients had unilateral and single metastases. Bilateral breast metastases from ovarian cancer have been reported in only 10 cases.[11]

Patients are typically diagnosed by clinical examination after presenting with a palpable breast lump or unilateral breast enlargement. More rarely, breast metastasis is detected as an incidental finding in women presenting for a mammography. In these patients, it may be difficult to distinguish a breast metastasis from a primary breast cancer. In patients with a known history of cancer, multiple masses or a solitary mass in the absence of calcifications on a mammogram should raise the suspicion of metastatic disease to the breast and warrants further evaluation.[6] Given the rarity of metastases to the breast coupled with the prevalence of primary breast cancer, even in the presence of a past history of an extramammary cancer, a breast mass is likely to represent a new primary breast tumour. Thus, it is recommended that a diagnostic bilateral mammogram and an ultrasound be performed and followed by percutaneous core biopsy to establish a tissue diagnosis.

Imaging studies are not always accurate in determining the correct diagnosis. In many cases imaging studies are mistakenly interpreted as a primary breast cancer or a benign lesion.[8,12] A contributing factor to these interpretations is the fact that the majority of these tumours presented as a solitary lesion in the breast. In contrast with primary breast cancer, at mammography, metastatic disease to the breast most commonly does not demonstrate speculated margins but appears as a single round or oval mass with circumscribed margins without skin or nipple retraction and rarely has associated calcifications. When calcifications occur, they are more commonly in patients with ovarian cancer.[13] At ultrasound examination the breast metastasis is usually hypoechoic with posterior acoustic enhancement and internal vascularity. With magnetic resonance imaging, a breast metastasis from extramammary origin usually appears as a round or oval circumscribed mass. The mass is typically isointense to normal breast parenchyma on both T1- and T2-weighted images, with homogeneous enhancement on post-contrast images. Breast metastases may be incidentally identified with computed tomography imaging, as it is commonly performed for many indications, including staging and follow-up of neoplastic disease. Computed tomography shows an around or oval well-defined mass, often with circumscribed margins, which typically enhances after contrast administration. Positron emission tomography is another common tool for disease staging and monitoring neoplastic disease progression and response to therapy that can show incidentally metastatic disease to the breast. The fluorodeoxyglucose uptake of the breast metastasis usually mirrors that of the primary tumour. A breast mass identified with positron emission tomography should prompt dedicated breast imaging with diagnostic mammography and breast ultrasound.[13-15]

At histological examination, metastases typically do not have an invasive ductal or in situ

component, while they often have a relatively well-circumscribed growth pattern surrounded by a fibrous pseudocapsule.[8,12,16,17] Additionally, calcifications are usually absent, although 'psammomatous' calcifications may be observed in serous ovarian carcinoma.[10,18] In patients with a history of cancer, it is useful for the pathologist to review slides from the primary tumour and compare the primary histology with that of the suspicious breast lesion. This is particularly true in cases diagnosed by fine-needle aspiration or those in which there is unusual histology.[19] Armed with histology from a previous cancer, the pathologist can often differentiate a primary breast tumour from metastasis to the breast. Immunohistochemistry can be very valuable when trying to differentiate between a primary cancer originating in the breast and a metastasis to the breast.[8,17,20] In the case of ovarian cancer metastasized to the breast, staining for WT-1 may be helpful,[10] as in our case. Although no marker should be considered 100% specific, these markers, along with comparison of pathology from the primary tumour and the suspicious breast lesion, can help to differentiate between a primary cancer and metastasis to the breast. In the near future, newer technologies, such as gene-expression profiling, may help further elucidate the tissue of origin in patients with an unknown primary.

While systemic treatment according to the primary tumour histology is usually administered to these patients, wide local excision of the tumour or mastectomy may be considered in patients with metastatic disease limited to the breast, or with minimal disease burden elsewhere.[6] In a recent series,[6] the overall survival in patients who underwent surgery was significantly better (15.5 months vs. 8.1 months, p=0.0001). This was also observed in multivariate analysis (p<0.001), but a selection bias cannot be ruled out. It is likely that patients with clearly advanced disease or those in poor health were spared surgery. In addition, disease status likely reflects the inherent survival advantage of patients with favourable histology who have no evidence of disease at presentation. Further data are needed to determine whether surgical resection of breast metastases in the setting of limited metastatic disease may result in a survival advantage. In the present patient, performance of mastectomy will be considered when the recurrent disease remains limited to the right breast.

The prognosis is poor with a median duration of survival from diagnosis of breast metastasis of 10-15 months, reflecting the biology of disease.[7,8] Most patients present with a breast lump as their chief complaint but also have concomitant widespread systemic metastases. In a series of patients with extramammary breast metastasis,[6] histological type, the absence of disease elsewhere and surgical intervention were all significant predictors of survival on univariate analysis.

Despite the high incidence and prevalence of primary breast cancer, metastasis from extramammary origin should be suspected in patients with a prior history of another malignant tumour. It occurs in an age group at high risk for primary breast cancer and can be misdiagnosed if not considered. Its recognition is important because the prognosis and treatment differ greatly from that of primary breast cancer. Given the poor prognosis of metastatic disease, the treatment should be individualized. In patients with metastatic disease limited to the breast, or with minimal disease burden elsewhere, wide local excision of breast metastases or mastectomy may be considered.

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