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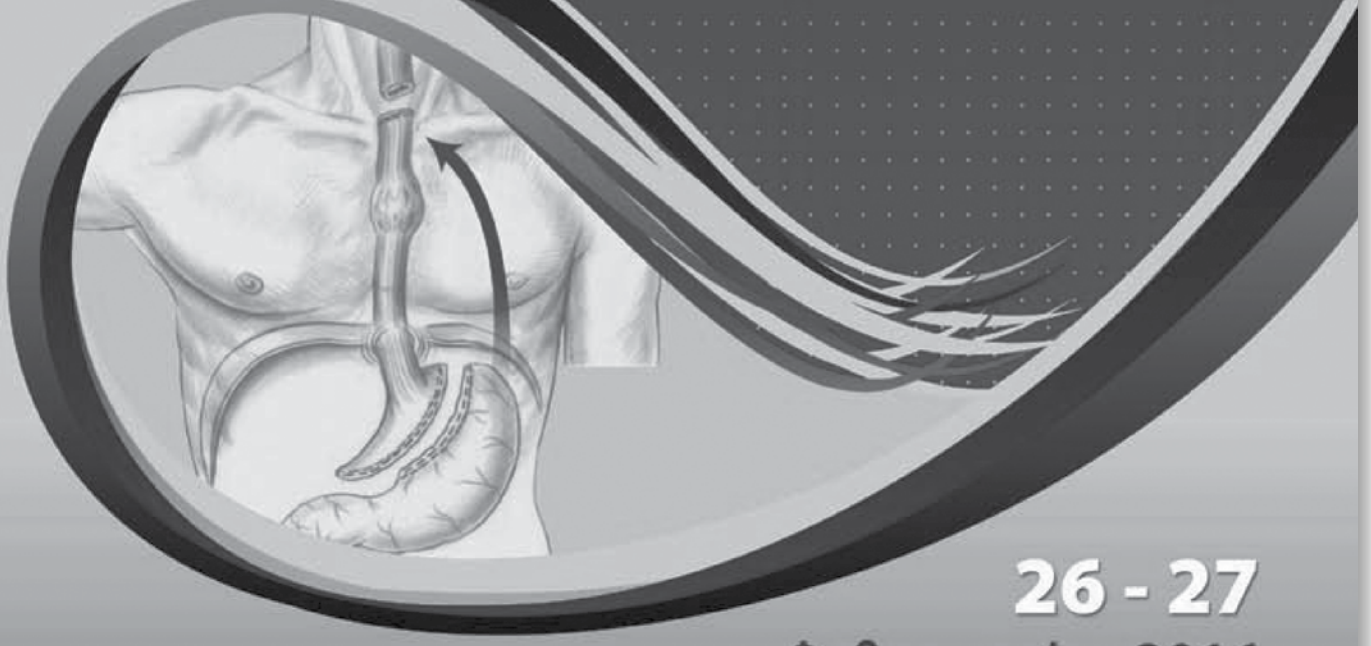

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REVIEW

A comparison between surgical management of cutaneous melanoma localized in the head and neck region and those at other sites

E. de Bree,[1] I. Gkionis,[2] D. Kassotakis,[1] R. de Bree[2]

[1]Department of Surgical Oncology, Medical School of Crete University Hospital, Heraklion, Greece, [2]Department of Surgery, Venezeleio General Hospital, Heraklion, Greece and [3]Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, Utrecht, The Netherlands

ABSTRACT

Despite the evolving progress in the systemic treatment of cutaneous melanoma, the mainstay treatment of melanoma continues to be surgery. The surgical treatment of clinically localized melanoma comprises wide local excision and, in most cases, sentinel lymph node biopsy, while in the case of regional lymph node metastases in the absence of systemic disease, lymphadenectomy is indicated. However, surgical treatment may be altered due to the anatomic constraints in the head and neck region. Also, the natural biology of melanoma in this region of the human body may be different, which subsequently results in a different prognosis and the need for adjusted management. From non-randomized studies, it seems that margins may be somewhat reduced, as opposed to current general practice guidelines, in order to preserve critical anatomic structures without any significant increase in the local recurrence rate. Regarding the sentinel lymph node biopsy, it seems that these MSLT-1 data are applicable to head and neck melanomas without major restriction. Despite the fact that sentinel lymph node biopsy in cutaneous head and neck melanoma when compared to other sites is less accurate, has a lower identification rate and a high false negative rate, is less frequently positive and overall survival for head and neck melanoma is poorer, it does offer detailed staging, substantial regional disease control and major prognostic information. Because its status remains of highly significant prognostic value, the sentinel lymph node biopsy procedure is of importance in selecting patients for eventual adjuvant systemic treatment and in defining patients for research studies. Since the advantages of the procedure and its morbidity in the head and neck are generally comparable to those of other sites, indications similar to those of other sites should be used for sentinel lymph node biopsy in head and neck melanoma. In head and neck melanoma with nodal metastases, the extent of neck lymph node dissection is still a matter of ongoing debate. Preferably, it should be tailored to the individual patient and be dependent on surgery induced morbidity and the risk of missing additional lymph node metastases. Lymphoscintigraphy may be helpful in limiting the extent of lymph node dissection without impairing regional disease control while potentially decreasing morbidity.

KEY WORDS: melanoma, head and neck, surgery, margins, sentinel node biopsy

Corresponding author
Eelco de Bree, MD, Department of Surgical Oncology, University Hospital, P.O. Box 1352, 71110 Heraklion, Greece, Tel.: +30-2810-392056 / 392382, Fax: +30-2810-392382, e-mail: debree@edu.uoc.gr

INTRODUCTION

Cutaneous melanoma is the fifth and seventh most common malignancy and constitutes 5% and 4% of the malignancies in males and females, respectively, in the U.S.A.[1] The life-time risk of developing an invasive melanoma has been estimated to be 3.0% and 1.9% for male and female Caucasian U.S.A. citizens, respectively.[1] However, due to the fact that more than 80% of patients are initially diagnosed with localized disease, melanoma is fortunately not among the ten leading fatal cancer types, either for males or for females.[1] Survival of melanoma patients is highly related to the presence of distant metastases, the nodal status, the presence of in-transit or satellite lesions, Breslow thickness, the presence of ulceration and increased number of mitoses.[2] Regarding the nodal status, it is not only important whether, but also, how many, lymph nodes are involved. Moreover, the tumour load of the lymph nodes is of prognostic value, for example clinically involved nodes (macro-metastases) or detected with sentinel node biopsy lymph node metastases (micro-metastases).[2]

Despite the evolving progress in systemic treatment of cutaneous melanoma, the mainstay treatment of melanoma continues to be surgery. The surgical treatment of clinically localized melanoma concerns wide local excision and, in most cases, sentinel lymph node biopsy, while in the case of regional lymph node metastases in the absence of systemic disease, lymphadenectomy is indicated. However, surgical treatment may be altered due to the anatomic constraints in the head and neck region. Also the natural biology of melanoma in this region of the human body may be different, which subsequently results in a different prognosis and need for adjusted management. In this review, the surgical management of cutaneous head and neck melanoma in comparison to that of cutaneous melanoma at other sites, is discussed.

DIFFERENCES BETWEEN HEAD AND NECK LOCALIZATION AND OTHER SITES

Surgical margins

After diagnostic biopsy of a suspicious mole that turns out to be a melanoma, a complementary therapeutic re-excision is necessary to remove potentially present microscopic satellite metastases. Most oncologic societies advocate that melanomas with ≤1 mm Breslow thickness should be re-excised with 1 cm margins, with 1 or 2 mm Breslow thickness with 1-2 cm margins and with ≥2 mm Breslow thickness with 2 cm margins.[3-6] These guidelines are based on various randomized trials.[7-13]

However, the proximity of head and neck cutaneous melanomas to critical anatomic structures requires that the surgeons achieve a balance between adequate margins of excision and the functional and aesthetic needs of patients. The delicate anatomy of the head and neck, especially of the face, often limits the ability to obtain wide surgical margins. Regarding the width of the complementary therapeutic (re-)excision there are no specific data from randomized trials available for cutaneous head and neck melanoma. In most of the classical randomized trials that investigated the minimal width of the surgical margins of the re-excision,[7-12] head and neck cutaneous melanomas were excluded. Only in the French trial[13] were patients with head and neck cutaneous melanoma included. However, they comprised only 16 of the total 326 patients. This small number is not unexpected since in this trial patients were allocated to 2 cm or 5 cm margins and the latter width is hardly possible in the head and neck region. No separate data regarding disease recurrence were provided for the various sites. In a retrospective study,[14] no statistically significant difference in local recurrence rate was observed between various widths of the surgical margins (<1 cm, 1-2 cm and >2 cm) in 104 patients with melanoma on sites of the

face. In a recent study,[15] 79 patients with primary cutaneous head and neck invasive melanoma who were treated with wide local (re-)excision were prospectively assessed for local recurrence. While 42 wide local excisions were performed according to current guidelines (see above), reduced margins (0.5 cm for ≤1.0 mm thickness, 0.5-1.0 cm for 1.01-2.0 mm thickness and 1.0 cm for >2.0 thickness) were utilized in 37 cases to preserve critical anatomic structures such as eyelid, nose, mouth and auricle. The overall local recurrence rate was 8.9% over a mean follow-up period and a minimum of 60 months. Reducing the margins of wide local excision did not significantly increase local recurrence rates (9.6% vs. 8.1%, p=0.806). In another retrospective study of eyelid melanoma,[16] the effect of the width of surgical margins on local recurrence was examined in 44 patients. A 5-mm margin of excision seemed to be adequate for thin melanomas of the periocular skin, but because of the small number of patients in this series who had >5-mm margins, a definitive comparison of outcome with larger margins of excision could not be made. For melanomas with Breslow thickness of ≥2 mm, wider margins of excision appeared to be prudent. Despite the potential higher risk of positive margins due to the limitations of wide excision in cutaneous head and neck melanoma, immediate reconstruction seems to be safe for the majority of patients with head and neck melanoma.[17,18]

Sentinel lymph node biopsy

In the MSLT-1,[19] melanoma patients without evident lymph node and systemic metastases were randomized between management based on sentinel node biopsy (60% of the included patients) and observation (40% of the included patients). In the observation-arm, patients underwent wide local excision and observation of the regional lymph nodes, with lymph node dissection being performed only when lymph node metastases became clinically evident. In the sentinel lymph node biopsy-arm, wide local excision was followed by sentinel node biopsy, with immediate lymph node dissection when involvement of a sentinel lymph node was found. In total, the results of the 2001 patients included in this study were analysed, with special focus placed on the intermediate thickness (in this trial defined as Breslow thickness 1.2-3.5 mm) and thick melanomas (Breslow thickness >3.5 mm). Interval analyses having previously been reported, the final results of a 10-year follow-up period were finally presented. Based mostly on the interim results of this study international recommendations were announced as with regard to the indications of sentinel lymph node biopsy.

The joint SSO-ASCO guidelines[20] recommend sentinel lymph node biopsy for intermediate-thickness cutaneous melanoma (Breslow thickness 1-4 mm) of any anatomic site. They stress that routine use of sentinel lymph node biopsy in these patients provides accurate staging. In thick melanomas (Breslow thickness >4 mm) sentinel lymph node biopsy may be recommended for staging purpose and to facilitate regional disease control. Regarding thin melanomas (Breslow thickness <1 mm), the procedure may be considered for selected patients with high-risk features when the benefits of pathologic staging may outweigh the potential morbidity of the procedure. According to these guidelines, such risk factors may include ulceration or mitotic rate ≥1 per mm^2, especially in the subgroup of patients with melanoma 0.75-0.99 in Breslow thickness. Finally, completion lymph node dissection is recommended for all patients with a positive sentinel lymph node until the data from the MSLT-2 trial, which investigates the benefit of completion lymph node dissection, are available.

Regarding the application of sentinel node biopsy, the question arises whether the data of the MSLT-1are uniformly applicable to melanomas of the head and neck region. In the final report of the MSLT-1,[19] data have not been provided, either regarding the proportion of head and neck melanoma included in the study or regarding the

specific sentinel node positivity and outcome of the subgroup of patients with melanoma located in the head and neck area.

The sentinel lymph node identification rate is significantly lower in the head and neck region than at other sites. In the final report of the MSLT-1 study at least one sentinel was identified in more than 99% of all melanoma patients, whereas in a recent systemic review the sentinel node identification rate in head and neck melanoma was calculated to be 94%.[21] In a previous report on a different population of the MSLT-1 study,[22] the identification rate was 99.3% for the groin, 95.3% for the axilla and only 84.5% for the neck basins. This considerably lower identification rate may frequently be due to the short distance between injection site and the yet to be detected sentinel lymph node ('shine-through effect': the high radioactivity at the primary site after injection of the radiotracer may obscure that of the sentinel lymph nodes), the complex lymph drainage and anatomy, and the much smaller than usual size of the lymph nodes in the head and neck region.

There are data from a recent study which specifically investigated whether head and neck melanoma is different from trunk and extremity melanomas with respect to sentinel lymph node status and outcome. In this study with a large number of melanoma patients (n=2,079) and an adequate follow-up period (median 6.7 years),[23] it appeared that the primary melanoma anatomic location is an independent predictor not only of recurrence risk and death, but also of sentinel lymph node status. The primary melanomas were located on the extremities in 43.3%, on the trunk in 39.4% and in the head and neck area in 17.3% of the cases. Although the mean melanoma thickness and mitotic rate did not differ significantly between the three groups (p=0.086 and p=0.571, respectively), the incidence of ulceration was only slightly increased in extremity melanoma (p=0.038) and the Clark's level of invasion was even significantly higher in head and neck melanomas, the rate of metastatic involvement of the sentinel node was considerably lower in head and neck melanomas than for localization on extremities and trunk (10.8%, 16.8% and 19.3%, respectively; p=0.002). In logistic regression analysis, head and neck melanoma was significantly less likely to have sentinel lymph node metastases compared with extremity and trunk melanoma (p=0.001), especially for melanomas with tumour thickness >2.0 mm. Nodal recurrence after negative sentinel node biopsy was significantly more frequent in the head and neck region than at other sites. While 12.8% for all sites, the false negative rate was 29.1% for head and neck melanomas. This higher false negative rate and the above noted lower identification rate, may similarly be attributed to the complex and often multiple lymph drainage pathways, the complex anatomy, the close proximity of the primary melanoma (injection site) and the much smaller than usual size of the lymph nodes in the head and neck region. Although in head and neck melanoma the sentinel lymph node was less frequently involved than in melanoma at other sites and while the sentinel lymph node status is known as one of the strongest prognostic factors for melanoma-specific survival,[19] the risk for disease recurrence and death was substantially higher in head and neck melanoma when compared to both extremity and trunk melanomas.[23] It may be that the rich vascularity of the head and neck, especially of the scalp, may allow for increased risk of direct haematogenous dissemination and consequently for impaired outcome, in the absence of invasion of the lymphatic vessels.[23] After adjusting for age, gender, race, sentinel lymph node status and ulceration, head and neck melanoma was found to have a significantly lower rate in disease-free survival (HR 0.45, p<0.001) and overall survival (HR 0.51, p<0.001) when compared with other locations.[23]

Bearing the above in mind, one may conclude that sentinel lymph node biopsy in clinically localized melanoma of the head and neck region may provide a smaller likelihood of survival benefit and

be of less prognostic value than at other locations, since the frequency of sentinel node positivity is significantly smaller, the false negative rate of the procedure is much higher and independent of the sentinel node status survival, is significantly impaired for head and neck melanoma when compared with melanomas at other sites. While in a SEER database analysis[24] and in a large retrospective single centre study[25] no survival benefit could be demonstrated for sentinel lymph node biopsy in head and neck melanoma patients, in a recent non-randomized comparative study[26] of head and neck melanoma patients, sentinel lymph node biopsy and subsequent lymph node dissection in sentinel lymph node positive cases was associated with a strong trend towards increased disease-specific survival (HR 1.56, p=0.053) and a statistically significant increase in disease-free (HR 1.59, p=0.011), lymph node metastasis-free (HR 2.04, p=0.007) and distant metastasis-free survival (HR 1.72, p=0.015) when compared with the observation arm management.

Nevertheless, in clinically localized head and neck melanoma, the sentinel node status has been found to be a very strong independent prognostic factor for disease-free and overall survival.[23,26,27] Thus, sentinel lymph node biopsy remains a highly significant prognostic tool in head and neck melanoma.

Clinical judgment must be used when considering sentinel lymph node biopsy in patients with comorbid medical conditions. The individual risks and benefits of the procedure should be weighed against the operative and aesthetic risks as well as potential competing causes of mortality. Moreover, as mentioned, the potential benefit of sentinel node biopsy should be weighed against the morbidity and costs of the procedure. This is especially applicable in the cases of thin melanomas, in which the chance of nodal involvement is very low. Generally, the morbidity of the procedure is infrequent and minor.[22] The most frequent morbidity comprises wound complications which have been observed in approximately 10% of patients and include dehiscence (1.2%), infection (4.6%) and seroma/haematoma (5.5%), and were easily treated with wound care and selective use of antibiotics. In a recent study of sentinel node biopsy in head and neck melanoma, no permanent nerve injury was observed.[27] Even if one may have some concern regarding the morbidity of performing a biopsy of sentinel lymph nodes located in the parotid gland, parotid-sparing sentinel lymph node biopsy can be carried out in a safe and efficient manner without affecting the regional recurrence rate or postoperative morbidity.[28] Hence, it appears that a sentinel lymph node biopsy in head and neck melanoma is associated with low and minor morbidity, similar to that of other sites. Since the advantages and morbidity of the procedure in head and neck melanoma are still generally comparable to those of other sites, similar indications should be used for sentinel lymph node biopsy in head and neck melanoma.[27-29]

Completion lymph node dissection of the neck

In approximately 20% of the head and neck melanoma patients with a positive sentinel node, additional involved nodes are found at completion cervical lymph node dissection.[30] This percentage is similar to completion lymph node dissection for melanoma at other sites and currently underlines the need for removal of additional nodes for regional disease control in the case of sentinel node metastasis. The ongoing MSLT-2 trial investigates whether this completion is actually necessary in all cases. Moreover, lymph node dissection for clinically evident lymph node metastases has been associated with an increased frequency of wound complications when compared to selective lymph node dissection after a positive sentinel lymph node biopsy at any site.[31] This difference was not statistically significant, possibly due to the relatively small number of lymph node dissections. Also, clinically evident lymph node metastases were detected during follow-up in the context of a randomized trial which is, obviously, often more rigorous than in everyday practice, allowing

for nodal recurrences to be detected as early as possible and before bulky nodal disease develops. Unfortunately, no separate analysis for cervical lymph node dissections was provided. Due to the delicate structures next to the cervical lymph node basins, it is most likely that cervical lymph node dissection for clinically evident lymph node metastases during the observation arm management is associated with increased morbidity when compared to early lymphadenectomy after positive sentinel lymph node biopsy. Therefore, sentinel node biopsy and completion lymph node dissection providing early and substantial regional disease control seems warranted for melanoma in the head and neck area.

In head and neck melanoma with nodal metastases, the extent of neck lymph node dissection is still a matter of ongoing debate. Preferably, it should be tailored to the individual patient and be dependent on surgery induced morbidity and the risk of missing additional lymph node metastases. Two decades ago, the classic drainage patterns of cutaneous head and neck melanoma were extensively described in a clinical study by O'Brien et al.[32] Many lymphoscintigraphy studies have confirmed this clinically predicted drainage pattern of head and neck melanoma according to its location, but have also demonstrated unexpected drainage patterns in 8% to 43% of the patients, with the postauricular, subocciptal, contraletaral, and distant nodal areas being the most common sites of discordance.[33-37] Hence, lymphatic mapping may facilitate in focusing follow-up on the area of initial nodal involvement thus allowing for earlier detection of nodal disease and limiting the extent of lymph node dissection without impairing regional disease control while potentially decreasing morbidity.[37,38] Completion cervical lymph node dissection guided by the site of the second-tier node (the one which receives the lymph from the primary site after the sentinel node) at lymphoscintigraphy may possibly result in more reliable selective lymphadenectomy.[24,37]

CONCLUSIONS

The anatomic constraints in the head and neck region and the potentially different biology of cutaneous head and neck melanomas are two reasons why surgical management may be different than for other sites. The proximity of head and neck cutaneous melanomas to critical anatomic structures requires that the surgeons achieve a balance between adequate margins of the wide local (re-)excision and the functional and cosmetic needs of patients. From non-randomized studies, it seems that margins may be somewhat reduced, when compared to current general practice guidelines, in order to preserve critical anatomic structures without any significant increase in the local recurrence rate. Regarding the sentinel lymph node biopsy, it seems that these MSLT-1 data are applicable to head and neck melanomas without major restriction. Despite the fact that sentinel lymph node biopsy in cutaneous head and neck melanoma when compared to other sites is less accurate, has a lower identification rate and a high false negative rate, is less frequently positive, and overall survival for head and neck melanoma is poorer, it offers detailed staging, substantial regional disease control and major prognostic information. Because its status remains of highly significant prognostic value, the sentinel lymph node biopsy procedure is of importance in selecting patients for eventual adjuvant systemic treatment and in defining patients for research studies. With increased experience, improved collaboration among the disciplines involved and novel technical developments,[39-42] it is warranted to believe that the technique has now become more reliable than in previous studies, especially in the more intricate head and neck region. Since the advantages of the procedure and its morbidity in the head and neck are generally comparable to that of other sites, indications similar to those of other sites should be used for sentinel lymph node biopsy in head and neck melanoma. In head and neck melanoma with nodal metastases, the

extent of neck lymph node dissection is still a matter of ongoing debate. Preferably, the procedure should be tailored to the individual patient and be dependent on surgery induced morbidity and the risk of missing additional lymph node metastases. Lymphoscintigraphy may be helpful in limiting the extent of lymph node dissection without impairing regional disease control while potentially decreasing morbidity.

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REVIEW

The contemporary management of retroperitoneal soft tissue sarcoma

E. de Bree,[1] D. Michelakis,[1] I. Heretis,[2] D. Stamatiou,[1] C. Ioannou[3]

[1]Department of Surgical Oncology, [2]Department of Urology and [3]Department of Vascular Surgery, Medical School of Crete University Hospital, Heraklion, Greece

ABSTRACT

Retroperitoneal soft tissue sarcoma is a rare disease, with local recurrence appearing more often than soft tissue sarcoma of the extremities due to anatomic constraints, the thinness of the overlying peritoneum and the limited application of adjuvant radiotherapy. In contrast to most other malignant diseases, local recurrence is the leading cause of death for these usually low-grade tumours. In this review, the current state of the art management of retroperitoneal soft tissue sarcoma is discussed. Surgery remains the mainstay of treatment, but thorough preoperative assessment and planning is of outmost importance. There is growing evidence that an aggressive surgical approach, with liberal en bloc resection of adjacent organs and structures, increases local tumour control. Assessment of the definite role of preoperative radiotherapy is subject to an ongoing randomized trial.

KEY WORDS: retroperitoneal sarcoma, management, surgery

INTRODUCTION

Retroperitoneal soft tissue sarcomas are rare tumours, with an expected incidence of approximately 3 new cases per million inhabitants per year and comprising approximately 10-15% of all soft tissue sarcomas.[1,2] They usually reach a large size before being diagnosed. Their localisation, more expansive than infiltrative manner of growth, slow growth and low metastatic potential usually result in late presentation with symptoms. Surgery is the mainstay of curative therapy and local control is critical for a patient's outcome.[3] Nevertheless, the thinness of the peritoneum covering these tumours and the anatomic constraints in the peritoneum limit the ability to achieve wide resection margins, which is the goal in sarcoma surgery. As a consequence, local recurrence is more frequent after surgery for retroperitoneal than for extremity soft tissue sarcoma.[4-14] Unlike the case for extremity soft tissue sarcomas, local recurrence comprises the leading cause of death for retroperitoneal soft tissue sarcomas since most are low- to intermediate-grade tumours with non-metastatic biological behaviour.[4-14] The feasibility of surgery decreases with each further

Corresponding author
Eelco de Bree, MD, Department of Surgical Oncology, University Hospital, P.O. Box 1352, 71110 Heraklion, Greece, Tel.: +30-2810-392056 / 392382, Fax: +30-2810-392382, e-mail: debree@edu.uoc.gr

recurrence, and the patients eventually develop widespread abdominal disease which is incurable even with modern multidisciplinary approaches. While adjuvant radiotherapy has been proven to be of benefit in local tumour control of soft tissue sarcoma at other sites,[15,16] for retroperitoneal sarcoma this issue is controversial and is currently being evaluated prospectively.[17] As for all soft tissue sarcomas, adjuvant systemic chemotherapy is of limited value.[18-21] Therefore, neither adjuvant treatment modality is routinely used and surgery remains the primary approach.

CLINICAL PRESENTATION

As already mentioned, the retroperitoneal soft tissue sarcomas generally grow slowly and reach large sizes before being diagnosed. They are asymptomatic for a long period and are sometimes found incidentally during imaging for other reasons. When symptomatic, the symptoms and signs are mostly nonspecific and include abdominal discomfort or pain, and abdominal distension or mass (Figures 1 and 2). Less frequently, these tumours cause symptoms associated with obstruction or infiltration of the gastrointestinal or urinary tract.[4-14]

IMAGING

The standard imaging method for retroperitoneal masses is computed tomography or magnetic resonance imaging of the abdomen and pelvis with intravenous contrast administration (Figures 1-3). Magnetic resonance imaging is especially indicated in the cases of allergy to computed tomography intravenous contrast or other contraindication for computed tomography, Li-Fraumeni syndrome, pelvic tumours and for assessing the extent of the tumour at specific sites that are not clearly depicted on computed tomography. After the diagnosis has been established, computed tomography of the chest is sufficient for staging of the disease, since the lungs are the first sites to be involved in the case of distant metastases. In some rare instances, positron emission tomography, angiography, bone scan and brain magnetic resonance imaging are required before treatment.[3,22,23]

The differential diagnosis of a retroperitoneal mass particularly includes, besides soft tissue sarcoma, lymphoma, metastatic adenocarcinoma, germ cell tumour, paraganglioma and benign soft tissue tumours. Hence, it is of critical importance to obtain a correct diagnosis before initiation of any treatment since the therapy for these entities is completely different. For example, while radical surgery is indicated for soft tissue sarcomas, lymphoma should be treated with systemic chemotherapy and benign soft tissue tumours with limited surgery. Since imaging methods are rarely pathognomonic, diagnostic biopsy is strongly recommended.[22-24] Only when the imaging is pathognomonic, as might be in the case of liposarcoma, and no preoperative treatment is considered, such a biopsy may be omitted.

BIOPSY

As discussed above, histological examination after diagnostic biopsy of a retroperitoneal mass is essential. The retroperitoneal localisation of the tumour causes some difficulties, including difficult access, unfeasibility of excision of the biopsy track en bloc with the sarcoma (as generally recommended for sarcomas in order to avoid local biopsy tract recurrence) and a potential risk of peritoneal dissemination of malignant cells. To solve the problem of the difficult accessibility of the mass, to avoid biopsy of necrotic tissue and to obtain tissue from the most suspicious and poorest differentiated component of the frequently heterogeneous mass, multiple image-guided percutaneous coaxial core needle biopsies (14 or 16 gauge) has been considered the method of choice for obtaining tissue for histological examination.[3,22-24] Additionally, image-guided core needle biopsy does not increase the risk of local recurrence, when compared with omission of diag-

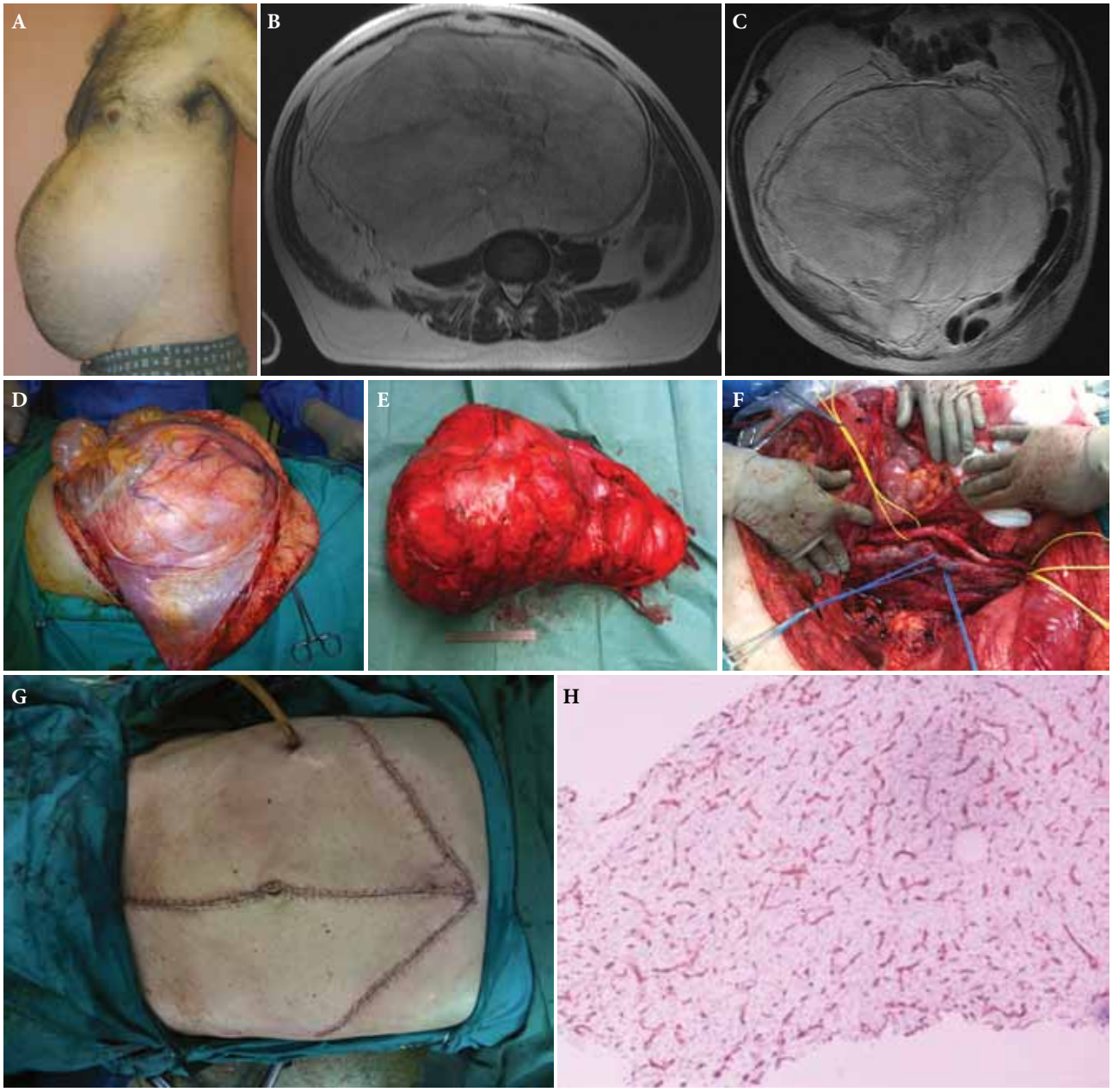

Figure 1. A 55-year old male patient with as only symptom of his retroperitoneal sarcoma, weighting 13 kg and measuring 45 cm in maximal diameter, abdominal distension (A). B and C: Magnetic resonance imaging showing the tumour. D: The large tumour at laparotomy. E: The surgical specimen. F: The abdominal cavity after resection of the tumour. G: The medial laparotomy with bilateral subcostal incisions required to resect the tumour. H: Histological examination demonstrating a myxoid liposarcoma.

nostic biopsy.[25] The risk of needle track seeding is minimal. When not diagnostic, repeat core biopsy with more aggressive sampling may be required. Open biopsy, with laparoscopic approach or by laparotomy, seems to have a similar diagnostic accuracy as image-guided core needle biopsy and does not increase the risk of local recurrence, but is associated with an increased risk of peritoneal dissemination, distortion of subsequent planes of dissection, possibility of not providing diagnostic tissue due to lack of three-dimensional imaging guidance, higher costs, more complications and

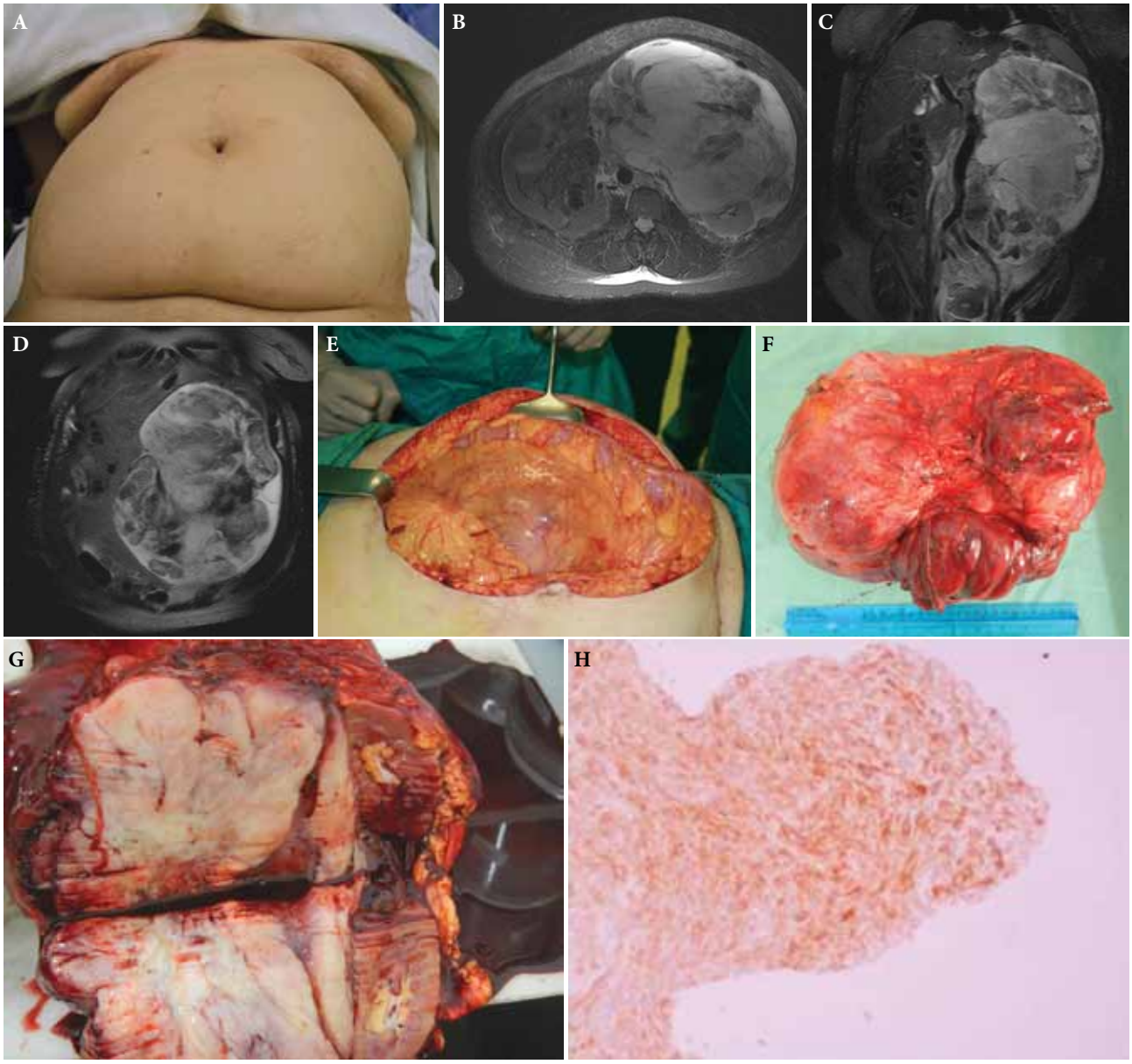

Figure 2. A 52-year old female patient with as only symptom of her retroperitoneal sarcoma, measuring 29 cm in maximal diameter, abdominal distension (A). B-D: Magnetic resonance imaging showing the tumour. E: The large tumour at laparotomy. F and G: The surgical specimen of the tumour with adjacent kidney and adrenal gland. H: Histological examination demonstrating an extra-gastrointestinal stromal tumour.

higher encumbrance for the patient.[3] Fine needle aspiration followed by cytological examination is rarely diagnostic.[3]

UNEXPECTED INTRAOPERATIVE FINDING

If at open or laparoscopic surgery for another reason, for example a suspected adnexal mass or hernia repair, a retroperitoneal mass is unexpectedly detected, it is recommended that nothing further to be done at that time. The patients should first undergo dedicated imaging. If appropriate imaging studies are already available at the time of surgery, open core needle biopsy can be considered but should be performed in a way that minimises

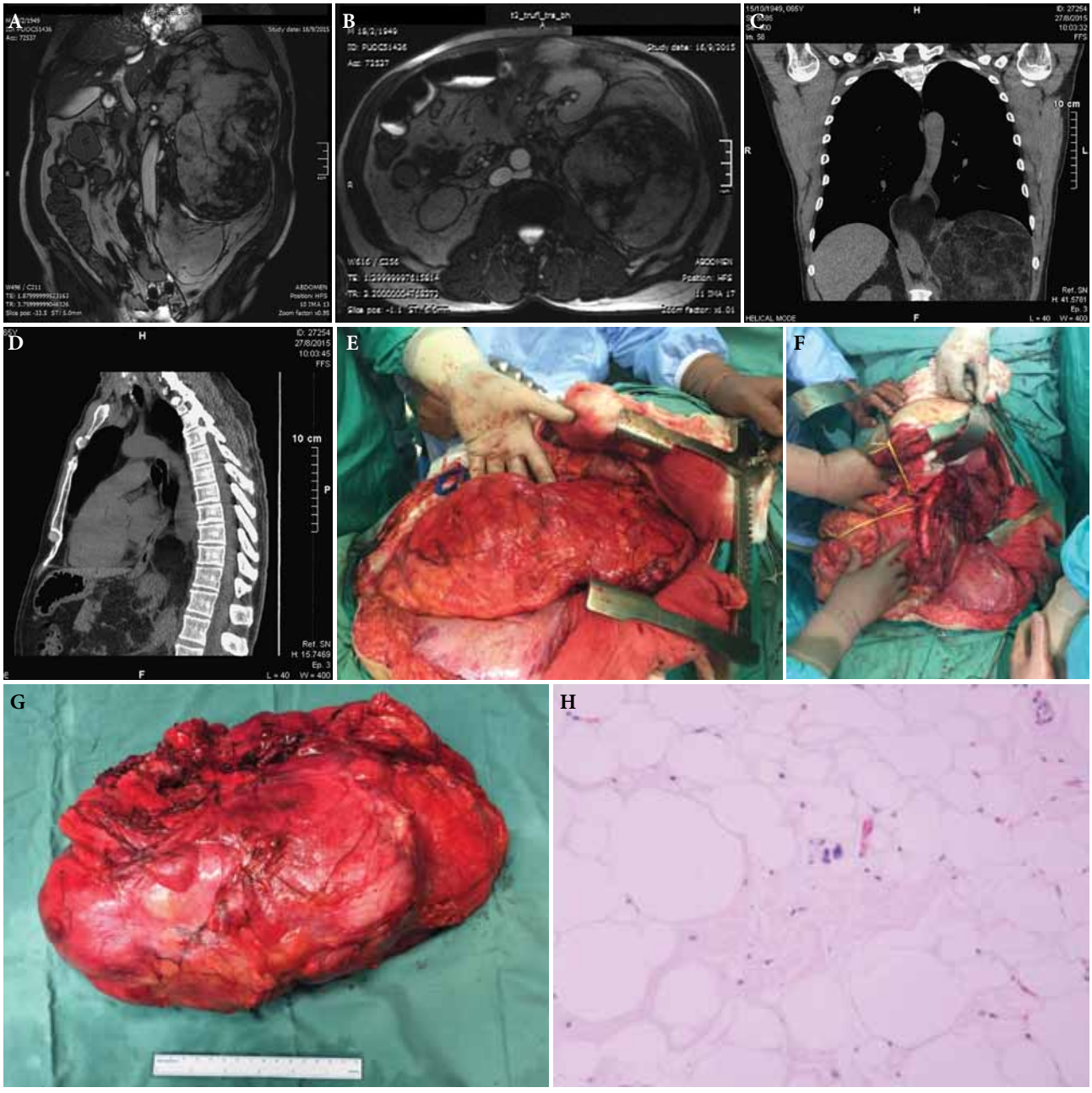

Figure 3. A 67-year old male patient with a large retroperitoneal sarcoma with displacement of the left kidney just under the abdominal wall at magnetic resonance imaging (A and B) and extension into the chest at chest computed tomography (C and D). E: The large tumour at laparotomy. F: The surgical specimen. G: The abdominal cavity after resection of the tumour. H: Histological examination demonstrating a well-differentiated liposarcoma.

the risk of peritoneal contamination and maximises the chance of obtaining adequate tissue samples. Frozen sections should not be based only on final pathology. If doubt exists as to these conditions, no biopsy should be performed intraoperatively.[3]

MANAGEMENT PLAN

The individual management plan should be determined after discussion at a multidisciplinary sarcoma case conference with presentation of both imaging and pathological findings.[16,17]

The multidisciplinary team should include a surgeon with experience in resection of retroperitoneal sarcoma, a pathologist, a radiologist, a radiotherapist, a medical oncologist and other surgical specialists according to the extent of the tumour.[3,23,26] Biological behaviour, response to treatment and clinical outcomes vary by histological subtype. The treatment plan, including the strategy for resection, should be developed in accordance with this and the stage of the disease.[27,28] Because retroperitoneal soft tissue sarcoma can grow to a very large size without causing symptoms, patients may present late with symptoms of mass effect, including malnutrition, shortness of breath and debility. Performance status should be assessed and taken into account as part of the development of an individual management plan. Nutritional support and physiotherapy may be required in conjunction with preoperative planning.

SURGICAL APPROACH

The best chance of resection with curative intent is at the time of initial presentation.[4-14] Complete gross resection is the cornerstone of management. In the case of primary retroperitoneal soft tissue sarcoma, surgery should be aimed at achieving macroscopically complete resection, with a single specimen encompassing the tumour and involved contiguous organs, and at minimizing microscopically tumour positive margins (Figures 1-3). However, as has already been noted, wide tumour resection is most frequently impossible due to the anatomical constraints in the retroperitoneal space and the thinness of the overlying peritoneum. Therefore, the local recurrence rate is significantly higher than for extremity soft tissue sarcomas. Especially for the low-grade retroperitoneal soft tissue sarcomas, local recurrence is the main cause of death.[4-14]

Preoperative evaluation should include assessment of the performance and nutritional status of the patient. The dedicated imaging studies should be studied meticulously. When various organs and structures are likely to require en bloc resection with the tumour, the different related surgical specialists should be consulted preoperatively. The multidisciplinary surgical team may frequently require, besides a surgeon with expertise in resection of retroperitoneal soft tissue sarcoma, a urologist and a vascular surgeon, while more rarely a thoracic surgeon, an orthopaedic surgeon, a neurosurgeon or other surgical specialist are warranted. The ability to orchestrate a team of complementary surgical experts is critical to successful management. When a kidney is at risk of concurrent resection, the renal function of the contralateral kidney should be assessed preoperatively by a differential nuclear renal scan. Further, the biological behaviour of the tumour is of importance in surgical strategy. While patients with high-grade retroperitoneal soft tissue sarcomas usually die of distant metastases and are less affected by local recurrence, low-grade tumours are prone to cause local recurrence in the absence of systemic disease. Therefore, also taking into account the lack of beneficial adjuvant treatment, a more aggressive surgical approach is advocated in low-grade retroperitoneal soft tissue sarcomas.[27-29]

The aim of macroscopically and microscopically complete resection is best achieved by resecting the tumour en bloc with adherent structures, even if they are not overtly infiltrated (Figures 2 and 3).[11-14] This concept is similar to that of resection of extremity soft tissue sarcoma with a rim of macroscopically normal tissue, which results in better margins and better local tumour control. Preservation of specific organs and neurovascular structures should be considered on an individual basis and mandates weighing the potential of local control against the potential for acute and long-term morbidity when resected. Ideally, the entire ipsilateral retroperitoneal compartment, including the macroscopically normal fatty tissue, should be cleared.[11-14,29] It is usually impossible to differentiate macroscopically normal fatty tissue

from low-grade liposarcoma, the most frequent histological subtype of retroperitoneal soft tissue sarcoma. Frozen section histological evaluation of marginal or suspicious fatty tissue is also not helpful intraoperatively.[3] The extent of resection of retroperitoneal liposarcoma should be guided by asymmetry shown on preoperative imaging, knowledge of anatomy and experience with patterns of recurrence. Moreover, retroperitoneal sarcoma appears to be multifocal or presents satellite lesions (Figure 4) in approximately 20% of the cases.[30-32] In these cases, complete resection of the retroperitoneal fatty tissue may diminish the risk of local recurrence.

An aggressive surgical approach

A more aggressive surgical approach, which is especially indicated for low-grade sarcomas, as outlined previously, has being advocated during the last few years.[11-14,29] While in the past in the case of adjacency of the kidney only its capsule was removed, nowadays most experts support the removal of the kidney en bloc with the tumour mass. The case is similar for en bloc removal of

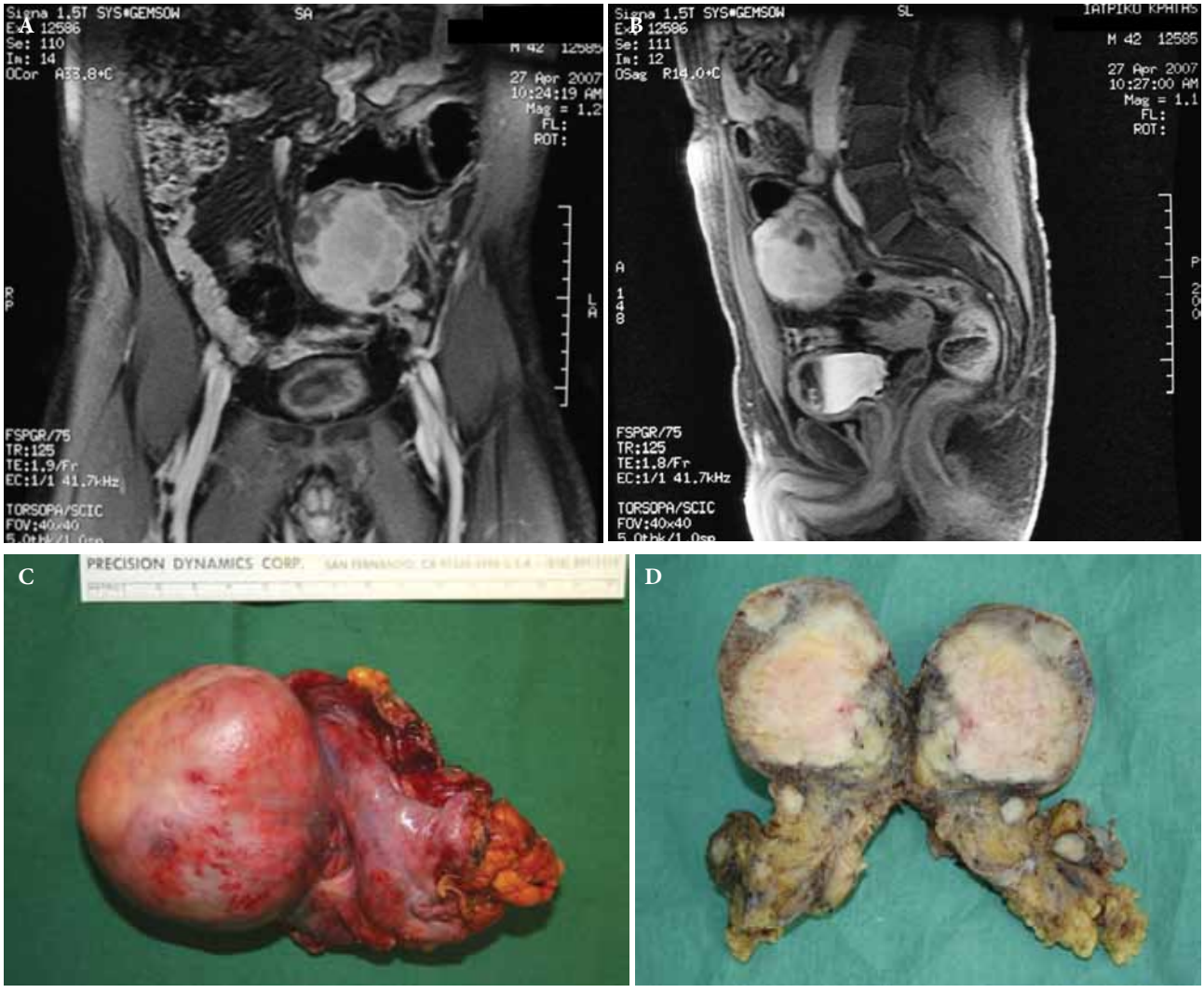

Figure 4. Magnetic resonance imaging of a retroperitoneal inflammatory myofibrosarcoma in a 42-year old male (A and B). Surgical specimen of the retroperitoneal tumour with satellite lesions (C and D).

adjacent bowel segments and spleen. Generally, with this approach, organs and structures of which removal en bloc with the tumour is associated with low morbidity are liberally sacrificed when the distance to the macroscopic tumour is less than 1 to 2 cm. These organs and structures include kidneys, small bowel, large bowel, psoas muscle, spleen, tail of the pancreas and diaphragm. In contrast, organs and structures whose resection is associated with increased morbidity, such as the duodenum, head of the pancreas, vertebrae and major vessels, are only removed en bloc with the tumour when they are overtly infiltrated. This aggressive surgical strategy appears feasible with acceptable morbidity and promising oncologic outcome.

Pioneers of this approach are the teams of Silvie Bonvalot (Institute Gustave-Roussy, Paris) and Alessandro Gronchi (Istituto Nazionale Tumori, Milan). In a retrospective nationwide French study of 382 patients with retroperitoneal soft tissue sarcoma treated from 1985 to 2005,[11] the association of type of surgery and outcome was analysed. Compartmental complete resection was defined as the systemic resection of tumour en bloc with uninvolved contiguous organs performed in order to obtain a rim of normal tissue surrounding the tumour (like muscles in limb sarcoma), thus ensuring optimal margins. Typically, the patient underwent an en bloc tumour resection of the overlying colon, the kidney inside and the psoas muscle at the back. The large vessels were exposed after removal of the adventitia, but the pancreas and duodenum were not resected when they were not involved. Systematic re-excision was defined as the reoperation with systematic remoal the colon, kidney and psoas muscle en bloc after previous gross total resection. In a multivariate analysis, complete compartmental resection was associated with an approximately two times lower risk of abdominal recurrence than after simple complete resection (p=0.04) or en bloc resection with involved contiguous organs (p=0.01). The risk of abdominal recurrence was almost twice as high after systemic re-excision, but this difference was not statistically significant (p=0.18) due to the small number of patients in this treatment group. The 3-year abdominal recurrence rates for the above surgical approaches were respectively 10%, 47%, 52% and 39%. In a multivariate analysis, other factors associated with decreased abdominal recurrences included low grade (p=0.008), no tumour rupture (p=0.0001), negative histological margins (p=0.008) and a high number of patients treated per centre (p=0.04). Centres operating on higher number of patients performed compartmental resection more frequently (p<0.0001) and had lower rates of intraoperative tumour rupture (p<0.0001) than at low-volume centres. However, while in univariate analysis the complete compartmental resection was associated with a four times better overall survival, type of surgery was not a statistically significant predictive factor for overall survival in multivariate analysis. In multivariate analysis, low grade, negative surgical margins, absence of tumour rupture and absence of gross residual disease were associated with increased overall survival.

In another retrospective study,[12] the results of surgery for retroperitoneal soft tissue sarcoma in the Istituto Nazionale Tumori were analysed for the periods before and after adoption of this more aggressive surgical strategy with liberal en bloc resections of adjacent organs and structures (136 patients in 1985-2001 and 152 patients in 2002-2007, respectively). The local recurrence rate decreased from 48% in the early period to 29% in the more recent period of treatment (p=0.0074). In a multivariate analysis, the statistically significant determinants for decreased risk of local recurrence were more recent period of treatment (p=0.0237), lower tumour grade (p=0.0316) and histological subtype of liposarcoma (p=0.0021). In an analysis of subgroups according to the tumour grade, the trend towards better local tumour control for patients operated in the recent period was more pronounced for grade 1 and 2 and minimal for grade 3 tumours. Moreover, in analysis according to histological type, only patients with lipo-

sarcoma had better local tumour control in the recent period (p=0.0070). Regarding the risk of distant metastases, remarkably, a higher 5-year distant metastases rate was found in the recent period of treatment (22% vs. 13%, p=0.0125). This increased incidence of distant metastases was only observed for the high grade sarcomas. In an analysis of subgroups according to grade, no difference in terms of occurrence of metastatic disease was observed for grade 1 and 2 tumours between the treatment periods, whereas a highly significant increase in the number of patients with metastases in the recent period for grade 3 tumours was noted (p=0.0002). The explanation for this observation remains unclear. Factors such as immune depression after major surgery and the release of growth factors locally might be possible factors. However, the authors note that those who developed metastases were not over-represented among the fraction of those who underwent major surgery and, hence, they attribute this trend to a prognostic shift in the patient population. As expected, low histological grade and histological subtype (liposarcoma vs. leiomyosarcoma) were highly associated with increased distant-disease-free survival in a multivariate analysis. Although the 5-year overall survival was higher in the recent period (60% vs. 51%), the difference was not statistically significant. In general, the median follow-up period was too short in the recently treated group of patients (32 months) in order to demonstrate difference in long-term survival. With the aim of demonstrating survival benefit, the same centre reported in a later publication data after longer follow-up.[14] Frontline extended surgery (191 patients, 48 months median follow-up) was associated with 5-years overall survival of 67% and a 5-year local recurrence free survival of 72%, while after traditional surgery (140 patients, 127 months median follow-up) these rates were 48% (p=0.009) and 51% (p=0.001), respectively. The 5-year risk of distant metastases remained higher in the recently treated patients (25% vs. 12%, p=0.005). Again distant metastases were mainly observed in high-grade tumours and histological types other than liposarcoma. The above retrospective data support the opinion that aggressive surgery with liberal en bloc resections of adjacent organs and structures may not be beneficial for high grade tumours due to their tendency to give rise to distant metastases and subsequent death. In contrast, aggressive surgery seems to be valuable especially in patients with a grade 1 or 2 tumour or/and liposarcoma.

To demonstrate the safety of this novel surgical approach, both centres (Institute Gustave-Roussy, Paris and Istituto Nazionale Tumori, Milan) gathered their experience and analysed the data.[13] A total of 249 consecutive patients with retroperitoneal soft tissue sarcoma had been treated with a frontline aggressive surgical approach. Complete macroscopic resection of the tumour, with a median size of 7 cm, was 93%. The median number of resected organs en bloc with the tumour was two. The operative mortality was 3%, while postoperative morbidity requiring an invasive therapeutic procedure was noted in 18% of the patients and surgical re-intervention was necessary in 12% of the patients. Major morbidity included anastomotic leakage (9%), intra-abdominal abscess (4%), postoperative bleeding (2%), wound dehiscence (2%), pulmonary embolism (0.4%) and lower limb compartmental syndrome (0.4%). No patient received a permanent stoma and no patient developed renal failure or femoral neuropathy. An almost three-fold increased risk (p=0.007) of morbidity was observed when more than three organs were resected concomitantly. After adjustment for the number of organs resected, only resection of large vessels, the stomach and small bowel (i.e. duodenum) remained to be associated with increased morbidity. The most common removal of colon, kidney and psoas muscle was not associated with increased morbidity. Postoperative morbidity did not seem to have an adverse impact on oncologic outcome, neither on abdominal recurrence nor on distant recurrence. In general, the morbidity and mortality of this aggressive surgical strategy seems

comparable to that of major abdominal surgery. Regarding the chronic morbidity after multivisceral resection for retroperitoneal sarcoma, which includes usually resection of the psoas adjacent to the femoral nerve and nephrectomy, a majority of the patients exhibit some sensory impairment of the limbs, but severe chronic pain and lower limb functional impairment are rare.[33] Additionally, it appears that long-term renal function is not significantly impaired when nephrectomy is performed. Although a formal comparison with postoperative morbidity of a more conservative approach of retroperitoneal soft tissue sarcoma has never been systematically analysed, postoperative morbidity seems similar for both approaches.

Resection of major vessels is seldom necessary in surgery for soft tissue sarcoma of the retroperitoneum. Although in the above analysis vascular resection en bloc with the tumour was associated with increased morbidity, vascular resection to facilitate adequate resection of retroperitoneal soft tissue sarcoma has an acceptable long term patency rate of the vascular reconstruction. However, such a resection is associated with a high risk of distant spread. Although the encasement of the vascular bundle does not represent a contraindication to surgery, there is an association with a high metastatic risk by virtue of the locally advanced nature of the disease and this should be considered when planning treatment.[29,34-36]

The overall results of a major series of patients treated with surgery for retroperitoneal soft tissue sarcoma are summarized in table 1. It seems that superior results are observed after aggressive surgical surgery. Finally, it has to be stressed that, ideally, patients with retroperitoneal soft tissue sarcoma are preferably referred to referral centres, where the best (surgical) approach can be planned and where a higher morbidity than the mentioned above can be avoided.[3,26]

Incomplete and palliative surgery

Grossly incomplete resection of retroperitoneal soft tissue sarcoma is of questionable benefit and potentially harmful. It may only be indicated as a potentially palliative procedure in carefully selected patients, as for example, in symptomatic patients with irresectable indolent growing tumours.[3] Grossly incomplete resection is to be avoided in many cases with meticulous imaging review, careful planning and referral to another centre if warranted.[4-14] Palliative surgery without tumour resection may be indicated in the case of gastrointestinal obstruction or bleeding.[3]

Table 1. Results of studies on the treatment of retroperitoneal soft tissue sarcoma.

Study	Study period	Number of patients	Median follow-up (months)	Complete resection (%)	5-year overall survival (%)	5-year LR-free survival (%)
Traditional surgery						
Lewis et al[4]	1982-1997	231	28	80	54	59
Stoeckle et al[5]	1980-1994	145	47	65	49	42
Gronchi et al[6]	1982-2001	82	65	88	54	63
Hassan et al[7]	1983-1995	97	36	78	51	56
van Dalen et al[8]	1989-1994	143	122	55	39	NR
Lehnert et al[9]	1998-2002	71	89	70	51	59
Strauss et al[10]	1990-2009	200	29	85	69	55
Aggressive surgery						
Bonvalot et al[13]*	2000-2008	249	37	93	65	78

LR: local recurrence, NR: not reported
*: combined series of Institute Gustave-Roussy, Paris and Istituto Nazionale Tumori, Milan

Surgery for local recurrence

Surgery remains the treatment of choice for local recurrence in the absence of systemic disease. In the case of loco-regional recurrence, surgery may still reproduce what is done for primary retroperitoneal soft tissue sarcoma if the first operation consisted of a simple excision. Therefore, the above described aggressive surgical approach seems to be indicated for such cases.[14] Otherwise, when a liberal en bloc resection has preceded, the aim of the surgical procedure should be simply to achieve macroscopic complete resection which includes surrounding organs and structures only when overtly infiltrated.[3] The feasibility of surgery decreases with each further recurrence. The potential benefit of surgery of local recurrence should be weighed against the increased morbidity of secondary surgery. The chance of a new recurrence is increased after surgery for local recurrence, but is smaller when the time period from primary surgery to local recurrence is longer. The biological behaviour of the local recurrence should also be considered. In fast growing local recurrences, the benefit of surgery may be minimal or nil. A retrospective study[37] demonstrated that patients with local recurrences that grew less than 0.9 cm per month profit from surgery, while those with faster growing recurrences do not.

ADJUVANT RADIOTHERAPY

The role of adjuvant treatment, such as radiotherapy and chemotherapy, in the management of retroperitoneal soft tissue sarcoma remains controversial. Preoperative chemotherapy, chemotherapy combined with hyperthermia, external beam radiotherapy and chemoradiotherapy appear to be safe for well-selected patients and may be considered after careful review by a multidisciplinary tumour board.[38-47] This is particularly relevant in the case of technically unresectable or borderline resectable retroperitoneal soft tissue sarcoma that could potentially be rendered resectable by downsizing, and also for chemosensitive histological types such as synovial sarcoma and leiomyosarcoma of the inferior vena cava.[3]

In soft tissue sarcoma of the extremities, two randomized trials[15,16] have demonstrated that adjuvant radiotherapy decreases the risk of local recurrence significantly. There is still a lack of randomized trials of adjuvant radiotherapy for retroperitoneal soft tissue sarcoma, mainly due to its rarity and the long follow-up required due to its commonly indolent biological behaviour. Many studies have shown a decreased risk of local recurrence with adjuvant radiotherapy. A retrospective study of the French Cancer Federation Sarcoma Group[48] demonstrated an increase of 5-year local tumour control from 23% to 55% (p=0.0021) by adding radiotherapy to surgery. In a recent study,[49] the prospective database of a referral centre which did not use adjuvant radiotherapy (Memorial Sloan Kettering Cancer Center, New York) was compared with that of one who did routinely use adjuvant radiotherapy after resection of a retroperitoneal soft tissue sarcoma (Massachusetts General Hospital, Boston). The 36 patients who received adjuvant radiotherapy displayed a significantly higher 5-year local recurrence survival rate than those who only underwent surgery (91% vs. 65%, p=0.03 in multivariate analysis). However, the disease-specific survival was not significantly different (93% vs. 85%, p=0.3) and the perioperative morbidity was most significantly higher among the patients who also received radiotherapy (44% vs. 16%, p=0.004).

A major problem with adjuvant radiotherapy for retroperitoneal soft tissue sarcoma is its toxicity to the bowel and to a lesser extent to the kidney(s), the liver, the ureter(s), urinary bladder, spinal cord and major peripheral nerves. The toxicity may be decreased by intraoperative radiotherapy, preoperative radiotherapy, postoperative radiotherapy with a tissue expander keeping the small bowel outside the radiation field and modern radiotherapy technology such as intension modulated radiation therapy (IMRT)

with less radiation emitted to structures outside the target field.[50-59] Intraoperative radiotherapy may be used for margins considered at risk, but the field is usually too large for its practical complication and the dose that can be delivered too small to omit postoperative external beam radiotherapy. In a small randomized trial,[60] disabling radiation-related enteritis was significantly less frequent after 20Gy intraoperative and 35-40Gy postoperative external beam radiotherapy when compared with 50-55Gy postoperative external beam radiotherapy (13% of 15 patients vs. 50% of 20 patients, p=0<0.05). However, radiation-related peripheral neuropathy was much more frequent among those who received intraoperative radiotherapy (60% vs. 5%, p<0.001). Although, after more than 5 years follow-up, the local recurrence rate was lower in the intraoperative radiotherapy group of patients (40% vs. 80%, p=0<0.001), the median survival was similar for both groups of patients. An alternative approach to reduce toxicity is the administration of radiotherapy before, instead of after, surgery. Due to intact local blood circulation before surgery a lower radiation dose is sufficient, while a smaller radiation target field is adequate in the absence of wide surgical dissection planes. A lower dose and a smaller field reduce the radiation exposure to adjacent healthy organs and structures. Moreover, less small bowel toxicity is exhibited due to the tumour itself keeping the bowel outside the radiation target field and due to the lack of adhesions that may cause a bowel segment to be exposed to radiation during the entire radiotherapy course. Additional potential advantages of preoperative radiotherapy, when compared with postoperative radiotherapy, include decreased risk of intraoperative spread of viable malignant cells and tumour size reduction. The potential disadvantages are the delay of surgery, difficulty in histological examination in the case of major or complete response and increased wound complications. In extremity soft tissue sarcoma, a randomized trial[61-63] comparing preoperative with postoperative radiotherapy has demonstrated similar local tumour control with decreased long term morbidity (i.e. oedema, fibrosis and functional impairment), increased wound complication rate and a small unexplainable increase in overall survival. In the above mentioned retrospective analyses of surgery for retroperitoneal soft tissue sarcoma, the addition of pre- or postoperative radiotherapy reduced the risk of local recurrence with approximately 35-50%.[11-14] Radiotherapy seemed to provide additional benefit to local outcome even after aggressive surgery for retroperitoneal soft tissue sarcoma.[12-14,64] In one study,[14] the addition of radiotherapy to surgery was in a multivariate analysis associated with statistically significant increased overall survival. The EORTC is currently performing a randomized trial of aggressive surgery with or without preoperative intension modulated radiation therapy (STRASS, NCT01344018).[17] The results of this study are eagerly awaited.

ADJUVANT CHEMOTHERAPY

In general, adjuvant systemic chemotherapy is not of much benefit in (high-risk) soft tissue sarcoma.[18-20] No randomized study has included only retroperitoneal soft tissue sarcoma. In a meta-analysis of 18 randomized trials,[18] which included soft tissue sarcoma at any site, adjuvant systemic chemotherapy reduced the risk of local and overall recurrence significantly (p=0.02 and p=0.0001), but not of overall survival (p=0.09). Only patients who received the combination of doxorubicin and ifosfamide displayed a statistically significant benefit in overall survival (p=0.01). However, the 6% absolute increase in survival was achieved at the cost of considerable toxicity. In a recent multicenter randomized EORTC trial,[65] 301 patients with intermediate and high grade soft tissue sarcomas at any site underwent surgery alone or followed by systemic chemotherapy with doxorubicin and ifosfamide. No difference in overall and disease-free survival was noted. Therefore, adjuvant systemic chemotherapy has

not been routinely used for soft tissue sarcoma.

Preoperative or neo-adjuvant systemic chemotherapy has the potential advantages of avoidance of delay in starting systemic chemotherapy due to surgical complications, early treatment of micrometastases, reduction of tumour size and in vivo assessment of treatment response. Absence of response may warrant change of chemotherapy regimen, while the extent of (complete) response is a major prognostic parameter. In the single randomized trial[66] on the benefit of preoperative systemic chemotherapy for high-risk soft tissue sarcomas, retroperitoneal localisation was not included. The 5-year overall and disease-free survival were similar after surgery with or without preoperative systemic chemotherapy with doxorubicin and ifosfamide. Unfortunately, local recurrence was not separately analysed. In an interesting randomized trial[67] on the benefit of regional hyperthermia in perioperative systemic chemotherapy with etoposide, doxorubicin and ifosfamide for high-risk soft tissue sarcoma at any site, including retroperitoneal localisation, the response to induction therapy was improved (p=0.02), the disease-free survival increased (p=0.011) and the local recurrence rate decreased by approximately 40% (p=0.003) with the addition of regional hyperthermia to systemic chemotherapy. However, the overall survival was not altered. Recent subgroup analysis of patients with completely resected high-risk abdominal and retroperitoneal sarcoma demonstrated that the 76 patients undergoing systemic chemotherapy with regional hyperthermia experienced lower local and overall recurrence rates than the 73 patients who underwent only systemic chemotherapy (5-year local recurrence-free survival 56% vs. 45%, p=0.044; 5-year disease-free survival 34% vs. 27%, p=0.040).[47] Once more there was no difference in overall survival between the groups of patients. Moreover, the technology to perform regional hyperthermia is not widely available. Within a multimodal therapeutic concept for abdominal and retroperitoneal high-risk sarcomas, chemotherapy with regional hyperthermia is a treatment option beside radical surgery and should be further evaluated in future trials.

During the last years there is a trend not to give a standard regimen (i.e. doxorubicin and ifosfamide) to all high-risk soft tissue sarcomas, but to administer 'histology-driven' systemic chemotherapy, acknowledging the fact that not every histological subtype responds similarly to chemotherapeutics.[20,68,69] In order to increase the efficacy of systemic chemotherapy, some advocate giving, for example, trabectedin for myxoid liposarcoma, gemcitabine plus dacarbazine for leiomyosarcoma, ifosfamide plus etoposide for malignant peripheral nerve sheath tumour, high-dose ifosfamide for synovial sarcoma, gemcitabine plus etoposide for undifferentiated pleomorphic sarcoma and docetaxel or paclitaxel for angiosarcoma. The definite role of this approach has to be awaited.

PROGNOSTIC FACTORS

As shown in table 1, the 5-year overall survival after surgery for localised retroperitoneal soft tissue varies in different studies from 39% to 65% and the local-recurrence-free survival from 42% to 78%. There are various prognostic factors for overall survival.[4-14] As outlined above, some are surgery related such as margin status, tumour rupture during surgery and, most probably, aggressiveness of surgery, while other prognostic factors are tumour related, including size, grade and histological subtype. Further, the patient's age appears to be an independent prognostic parameter for survival. A nomogram has been developed for predicting 5- and 10-year overall survival in patients with retroperitoneal soft tissue sarcoma.[70]

CONCLUSIONS

Retroperitoneal soft tissue sarcoma is a rare tumour. Local recurrence after surgery is more frequent than after surgery for extremity soft tissue

sarcoma due to anatomic constraints, the thinness of the overlying peritoneum and the limited application of adjuvant radiotherapy. In contrast to most other malignant diseases, local recurrence is the leading cause of death for these usually low-grade tumours. The mainstay of treatment for retroperitoneal sarcoma is surgery. There is growing evidence that an aggressive surgical approach, with liberal en bloc resection of adjacent organs and structures, increases local tumour control. The management of localised retroperitoneal soft tissue sarcoma may also be improved by adequate preoperative imaging, correct execution of biopsy of the tumour, case discussion in a multidisciplinary team and optimal planning of surgical treatment. Complete resection of the tumour is generally achieved with en bloc removal of adjacent organs and structures in an experienced centre by a team of surgeons of various disciplines with adequate expertise. The results of an ongoing randomized trial to assess the feasibility and efficacy of preoperative radiotherapy are eagerly awaited. Currently, adjuvant chemotherapy seems to be of limited value.

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ORIGINAL PAPER

Extralevator abdominoperineal resection for rectal cancer
A preliminary experience

D. Stamatiou,[1] G.E. Kostakis,[2] D. Michelakis,[1] K.G. Spiridakis,[2] E.E. Sfakianakis,[2] M.E. Flamourakis,[2] E. de Bree,[1] O. Zoras,[1] M. Christodoulakis[2]

Department of Surgical Oncology, Medical School of Crete University Hospital, Heraklion, Greece and Department of Surgery, Venizeleion-Pananeio Hospital, Heraklion, Greece

ABSTRACT

Aim: Compared with lower anterior resection, conventional abdominoperineal resection for rectal cancer is characterized by worse oncological outcome due to the higher rates of involved circumferential resection margin and intraoperative bowel perforation. Recently, a more radical excision, known as extralevator, or cylindrical abdominoperineal excision has been introduced and has been associated with encouraging results as regards considering oncological outcome. In this study, we present our initial experience. **Material and methods:** Between November 2011 and October 2015, 24 patients with lower rectum (distal 6 cm of the rectum) adenocarcinoma underwent extralevator abdominoperineal resection. The surgical details and complications as well as the histological parameters of the specimen were studied. **Results:** Thirteen patients underwent open extralevator abdominoperineal resection, while 11 patients underwent laparoscopic operation. The mean operative time was 4 hours for the open procedure, and 4.5 hours for the laparoscopic procedure, including the intraoperative turning of the patient into the jackknife position. Pelvic floor reconstruction was performed using the omentum in 20 patients, biological mesh in 2 patients and retroversion of the uterus in 2 patients. The mean hospital stay was 7 days, ranging from 5 to 20 days. One patient underwent emergent laparotomy due to small bowel perforation on the first postoperative day, while 2 patients, who had undergone open procedure, developed protracted postoperative ileus. All were managed successfully using in a conservative way. No other major complications were observed. In all cases, the lateral histological margins were >2 mm, while the mean lymph node number was 14. **Conclusions:** In our preliminary experience, extralevator abdominoperineal resection of distal rectal cancer appeared safe and associated with adequate histological parameters, as in other studies performed so far. However, more randomized control trials with longer follow-up are required to prove the oncological superiority of the extralevator technique over the conventional technique.

KEY WORDS: rectal cancer, extralevator abdominoperineal resection

Corresponding author
D. Stamatiou, MD, PhD, Department of Surgical Oncology, University Hospital, P.O. Box 1352, 711 10 Heraklion, Crete, Greece, Tel.: +30-2810-392382, Fax: +30-2810-392382, e-mail: jpstamatiou@yahoo.gr

INTRODUCTION

The introduction and widespread adoption of total mesorectal excision (TME), has set the basis for rectal cancer surgery, leading to a significant improvement in survival and disease control.[1,2] Despite this significant surgical innovative technique, improvement in both local recurrence and survival after abdominoperineal excision (APE) of the rectum and anus, are not proportionate to the ones after anterior resection (AR).[3,4] APE is associated with higher incidence of positive circumferential resection margin (CRM) as well as intra-operative bowel perforation.[5,6] These two factors have been shown to be independently associated with increased local recurrence and decreased overall survival.[4,7] The involvement of CRM in APE is usually found at the level of the rectal levator muscles of the pelvic floor,[4] the area where the abdominal and perineal dissection phases meet. Indeed, a basic feature of APE is the formation of a specimen that is narrowed at the levator muscles level, creating a "waist", which explains the high rates of positive CRM in APE specimens. Furthermore, the modest operative view during the perineal phase of the conventional APE, which is performed in the supine position, has been suggested as a predisposing factor for intraoperative bowel perforation.[8]

In view of these issues, a more radical approach, which in fact mirrors the original operation described by Miles in 1908,[9] has recently been introduced so as to achieve a cylindrical specimen, lessen the risk of positive CRM, and consequently reduce local recurrence rate.[10] Early reports of this cylindrical, or extralevator, APE (ELAPE) technique, suggest the technique's potential for reduction of CRM involvement, perforation rate and local recurrence rate.[10,11] Thus the use of ELAPE has been widespread ever since.[8,12-14] The purpose of this paper is to present our preliminary experience in performing ELAPE. The surgical details and complications, as well as the histological parameters of the specimen were studied. The follow-up is generally too short to enable an in detail study of local recurrence and survival rates and, therefore, these parameters were not analysed.

MATERIALS AND METHODS

Between November 2011 and October 2015, 24 patients with lower rectum (distal 6 cm of the rectum) adenocarcinoma underwent extralevator abdominoperineal resection in the Department of Surgical Oncology of the University Hospital of Heraklion and the Surgical Department of Venizeleion Hospital of Heraklion. All patients had undergone preoperative Magnetic Resonance Imaging (MRI). Twenty patients had a T3 tumour according to MRI imaging, while 4 had a T2 tumour. All patients with T3 tumour underwent long-course neoadjuvant chemoradiotherapy with 45 Gy in 25 fractions with twice daily Capecitabine 900 mg/m^2.

Surgical Technique

The operative approach followed the basic principles previously reported.[10] In cases where the laparoscopic approach was engaged for the abdominal phase, a 4 port technique was used. Omentoplasty was performed through division of greater omental attachments to the transverse colon and ligation of the right omental vessels at their origin from the right gastroepiploic artery. An omental flap perfused by the left gastroepiploic artery, was thus formed. Once the omental flap had reached sufficient length so as to reach the pelvic floor, the left colonic dissection commenced, using the medial-lateral dissection technique. The inferior mesenteric vein was initially ligated, facilitating colon mobilization, while high ligation of the inferior mesenteric artery followed. After identification and preservation of the hypogastric nerves, the rectum was mobilized as far as the upper border of the coccyx. The dissection was terminated at the level of the seminal vesicles in men, and the cervix in women. The left colon was then divided, and a left sided colostomy in a pre-

marked location on the anterior abdominal wall was formed. The omental flap was sutured to the distal end of the divided colon so as to allow its delivery during the perineal phase, after extraction of the specimen. A drain was placed in the operative field, exiting from the right lateral abdominal wall, and the abdomen was finally closed.

Patients were subsequently turned to the prone (jackknife) position, and the perineal dissection was performed, following the principles described previously, including disarticulation of the coccyx from the sacrum and Waldeyer's fascia division,[10] permitting entrance into the abdominal cavity to meet the intra-abdominal dissection. The specimen was removed and pelvic floor reconstruction was performed. A closed suction drain was placed under the perineal skin, and the perineal incision was finally closed.

RESULTS

Thirteen patients underwent open extralevator abdominoperineal resection, while 11 patients underwent laparoscopic operation. The mean operative time was 4 hours for the open procedure, and 4.5 hours for the laparoscopic procedure, including the intraoperative turning of the patient into the jackknife position. Pelvic floor reconstruction was performed using the omentum in 20 patients, biological mesh formed by cross-linked porcine dermal collagen (Permacol®, Tissue Science Laboratories plc, Alsershot, United Kingdom) in 2 patients (Figure 1), and retroversion of the uterus in 2 patients (Figure 2). In all cases, the principles of fast-tract surgery were followed. The mean hospital stay was 7 days, ranging from 5 to 20 days. One patient underwent emergent laparotomy due to small bowel perforation on the first postoperative day, while 2 patients, who had undergone open procedure, developed protracted postoperative ileus. All were managed successfully in a conservative way. No other major complications were observed. All specimens had a cylindrical shape (Figure 3), and no intraoperative bowel perforation was noted. In all cases, the lateral histological margins were >2 mm, while the mean lymph node number was 14,

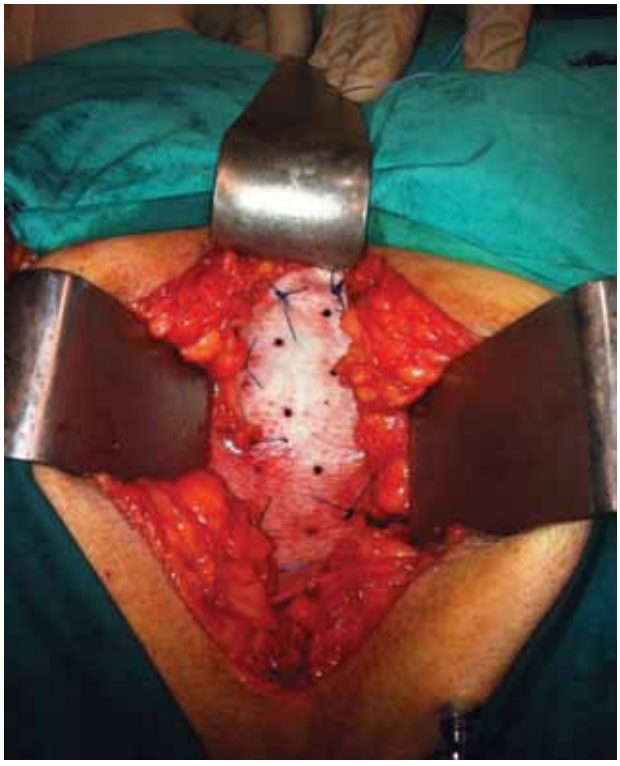

Figure 1. Pelvic floor reconstruction after extralevator abdominoperineal resection with biological mesh formed by cross-linked porcine dermal collagen.

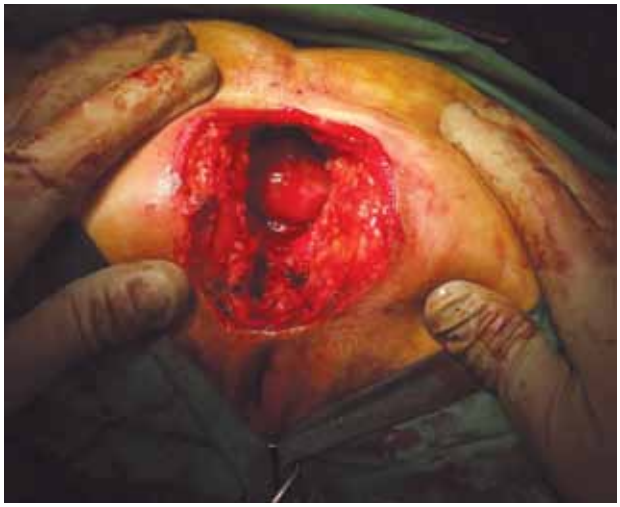

Figure 2. Pelvic floor reconstruction after extralevator abdominoperineal resection by retroversion of the uterus.

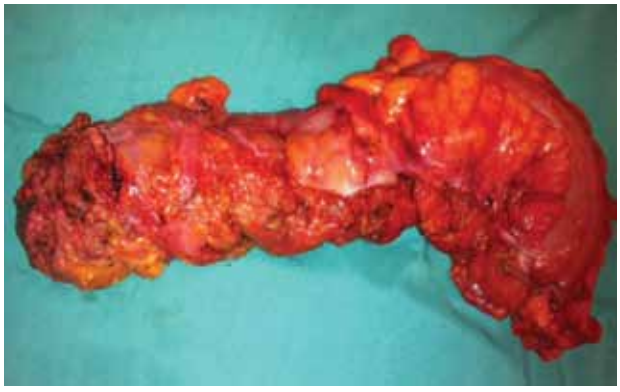

Figure 3. The cylindrical shape of the anorectal specimen after extralevator abdominoperineal reconstruction instead of the waist shape after traditional resection.

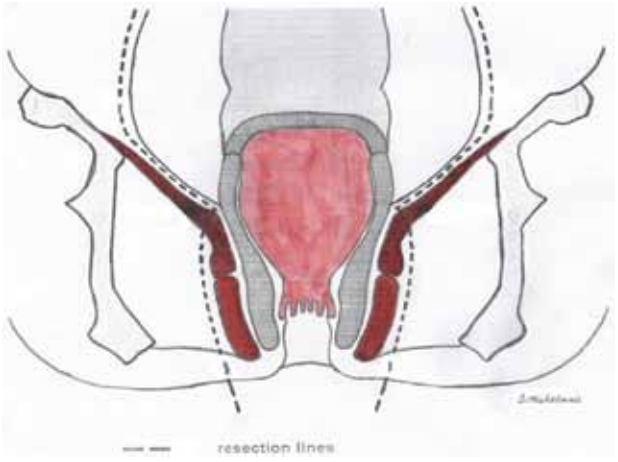

Figure 4. Schematic representation of the resection planes during conventional abdominoperineal excision.

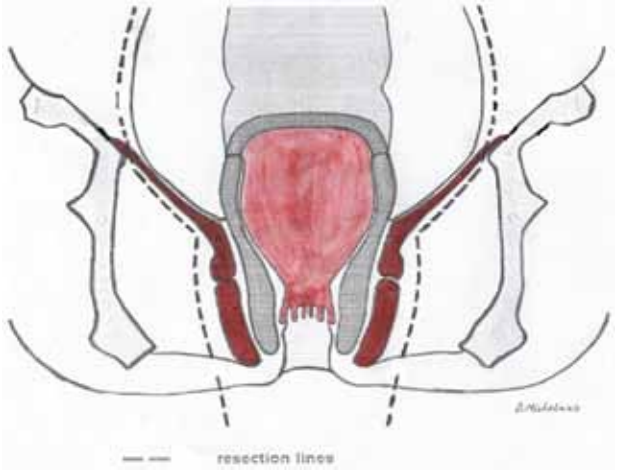

Figure 5. Schematic representation of the resection planes during extralevator abdominoperineal excision.

ranging from 5 to 34. A smaller number of lymph nodes were found in specimens of patients who had received neoadjuvant chemoradiotherapy. On recent follow-up, all patients remain free of disease, and have not developed perineal hernia.

DISCUSSION

The considerably inferior oncological results following conventional APE, compared with LAR, have called for surgical technique optimization by adopting an extended posterior perineal approach in order to avoid CRM involvement and intraoperative specimen perforation.[4,10] In conventional APE, the plane of dissection outside the mesorectum is followed to the top of the anal canal, with the latter lifted off the pelvic floor muscles (Figure 4). The resultant "waist" of the specimen, is the Achilles' heel of the operation, accounting for the adverse oncological outcomes. In the ELAPE, the perineal phase, which is performed in the prone position, includes identification of the levator muscles and continuation of the dissection along the muscles' outer surface, up to their insertion on the pelvic sidewall (Figure 5).[10] The basic anatomical differences between the conventional and the extralevator APE is that the mesorectum is not dissected off the levator muscles in the latter, and that the levator muscles are resected en bloc with the anal canal and lower rectum.[10] The resultant specimen is cylindrical, due to the fact that the levator muscle is still attached to the mesorectum, forming a cuff around the excised recto anal tube. The prone (jackknife) position, a distinct characteristic of the ELAPE, provides excellent view of the operative field, making the once difficult perineal phase of the procedure a lot easier to perform.[10]

In a recent meta analysis including 8 studies comparing conventional APE and ELAPE,[15] the oncological superiority of ELAPE, regarding recur-

rence rate, CRM involvement rate and intraoperative bowel perforation rate, were shown. During ELAPE, approximately 70% more tissue is removed outside the internal sphincter and muscularis propria in the distal 12 slices of the specimen (equating to the distal 6 cm), thus, significantly reducing CRM involvement.[11] Most of the extra tissue is located in the posterior aspect of the specimen, especially in cases where the coccyx is amputated. However, approximately 4 mm of extra tissue is also removed at the anterior and lateral aspects of the specimen, providing an adequate tissue barrier for anteriorly situated low rectal cancers that would have otherwise involved the CRM when the conventional technique had been used.[11] The significant reduction of bowel perforation during ELAPE, suggests a prerequisite, since many series have shown that perforation itself increases local recurrence and reduces survival.[4,16] Approximately 71% of perforated specimens harbour microscopic CRM involvement.[11] Although the majority of perforations have been reported to occur through the tumor,[4] more than 80% of perforations have been found in the anterior aspect of the specimen according to other studies, underlying the value of the cylindrical technique in this aspect.[11] All specimens of the present study had a cylindrical shape, no intraoperative bowel perforations were observed, while no case exhibited involved CRM.

Compared with conventional APE, ELAPE is more time consuming, a feature attributed both to the lack of experience and to the challenge of adapting this new technique and the intraoperative change of patient position for the perineal phase.[15] However, the improved direct visual scope derived from the placement of the patient in the prone position and the removal of the coccyx, simplifies the perineal dissection, and counterbalances the delay from the intraoperative change in patient's position, making faster ELAPE possible.[10]

Perineal wound complications, including infection and dehiscence, have classically suggested a significant issue after abdominoperineal resection, and are present at a rate of 35-66% after conventional APE, if primary closure is attempted.[17-20] Preoperative radiation adds to this risk, thus further increasing complication rate.[17] Resection of the muscles of the pelvic floor during ELAPE, leaving only fatty tissue and skin to cover a more extensive perineal defect, has the potential to further increase wound complications in the case of primary closure.[8,21] There is little information regarding optimal technique of perineal wound closure, following ELAPE.[21] Both biological meshes and myocutaneous flaps deriving from the gluteus maximus,[10,22-24] rectus abdominis and latissimus dorsi muscles[22,25] respectively, have been used, with no significant difference in complication rates between them. As yet, however, no high quality prospective trials have been conducted to compare the 2 methods.[15,21] The basic drawbacks from the use of myocutaneous flaps are donor-site related morbidity, increased operation time, and increased resources, since most of these reconstructions necessitate the contribution of a plastic surgeon.[21] The incidence of perineal hernia formation after perineal wound closure, using myocutaneous flaps (3.9%) or biological mesh (3.5%) are both low,[21] while other studies[23] did not report perineal herniation. In our series, biological mesh was used in 2 cases, while in 20 patients, omentoplasty was performed, and in 2 cases, the uterus was retroverted to fill the defect. Both of the latter 2 techniques have been reported,[8] but always with the addition of a biological mesh. No perineal hernia was noted in our series.

No significant difference in complication rates, especially urogenital dysfunction which constitutes the most common complication has been reported between APE and ELAPE.[15] Since sexual function is known to depend on the function and integrity of the pelvic autonomic nerves, and dysfunction may be caused either by damage at the level of the superior hypogastric plexus, the hypogastric nerves, or the inferior hypogastric plexus,[26] identification of the pelvic anatomic landmarks may potentially prove useful for the preservation of urogenital functions during ELAPE.

In conclusion, extralevator resection has recently presented as a more radical abdominoperineal resection for rectal cancer that seems to be oncologically superior compared to the conventional operation, without adding to patients' morbidity. For the above reasons, we have adopted this technique. Future randomised control trials with long-term follow-up are required to draw definitive conclusions regarding the superiority of ELAPE over the conventional technique.

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ORIGINAL PAPER

Patient classification system in a surgical oncology department

M. Astyrakaki, K. Anyfanti, C. Papadaki, S. Saridakis, O. Zoras

Department of Surgical Oncology, Medical School of Crete University Hospital, Heraklion, Greece

ABSTRACT

Aim: The purpose of the study is the evaluation of a surgical oncology unit based on summation of nursing duties. Material and Methods: The frequency of specific nursing duties, procedures or interventions was structurally observed in a surgical oncology unit of a tertiary hospital. Results: The time required for nursing procedures was calculated and patients were classified into groups based on specific factors. Also, through time tracking, these procedures were defined as specific activities and the allocation of time required by the nurses to fulfill them was determined. Conclusions: It is possible with the classification of patients into groups based on the severity of their condition to calculate the nursing workload and thus the resources required for caregiving by nurses and the allocation of time for the care of nurses and nursing assistants.

KEY WORDS: patient classification system, staffing nurses, disease severity index

INTRODUCTION

With the rapid developments in the health sector, issues such as quality provision of nursing services, hospitalization costs and patient safety are at the heart of both nursing research and international health organizations. To achieve quality nursing care and care objectives, it is essential to have a sufficient number of nursing staff, a figure that differs not only depending on the type of hospital, but also on the severity of the patients' condition in the individual departments of each hospital. For these reasons, patient classification systems have been developed in order to assess the number of nursing staff needed, to estimate the costs for each individual patient, to allocate patients, to form quality standards, to calculate budgets, to assess the level of services, to enhance the level of satisfaction between patients and nursing staff, and to provide nursing services in a safe environment.[1,2]

The purpose of the study is to describe the frequency of specific duties (interventions or processes) of nursing staff of the Department of Surgical Oncology at the University Hospital of Heraklion, Greece, in order to identify and investigate the characteristics of work load of nurses and assistant nurses.

Corresponding author
Marianna Astyrakaki, Department of Surgical Oncology, University Hospital, P.O. Box 1352, 71110 Heraklion, Greece;
Tel.: +30-2810-392304, Fax: +30-2810-392382, e-mail: astyrakaki@gmail.com

METHODS

The study design is typically descriptive and includes the description and measurement of time for nursing interventions and procedures in the Department of Surgical Oncology of the University Hospital of Heraklion, Greece. The research material results in the description of nursing operations, the calculated time for the above procedures and the assessment of the severity of patients' condition in the Department. The evaluation is based on the summation of functions.

Initially, in this research, the main investigators categorize nursing interventions and processes needed in the Department of Surgical Oncology. Thereafter, they categorize patients into four levels. The measurement methodology used is the structured observation, where specific interventions observed and which classified the patients into four categories:

I. Self-care/Minimal Care (patients awaiting diagnostic tests or surgery, low frequency therapeutic interventions, self-handling for everyday activities)
II. Moderate Care (patients requiring nursing supervision or assistance with mobility, moderate disease and recovery from serious illness/surgery)
III. Maximum Care (patients requiring close monitoring, nursing assistance for mobility, surveillance and enforcement activities and frequent or complex administration of therapy or medication)
IV. Intensive Care (emergencies, high degree of dependence on nursing, intensive care and treatment, unstable recovery path that requires frequent assessment and adjustment of treatment).

Based on the above categories the duration for each nursing intervention (minutes/hours) for each individual patient level was measured. In the end, the average time required by nurses and assistant nurses for each patient group was calculated.

The survey was conducted on 20 cases, of which 11 cases belonged to category I, 5 cases to category II, 3 cases to category III and 1 case to category IV. The survey participants were all nurses of the Department who had signed an informed consent. Anonymity and protection of their rights was assured and there was no interference in the care processes. The study was carried out beyond the nursing staff's work obligations.

The time that nurses of the Department need for patients' care was calculated in order to understand the distribution of time for both nurses and supporting staff required for direct and indirect care.

RESULTS

The total measured time of employment per shift for both nurses and assistant nurses is listed below and subsequently, the corresponding need of nursing staff is noted.

The required nurse staffing per shift:

Morning shift: 909 minutes = 15.15 hours = 2 nurses

Afternoon shift: 407 minutes = 6.78 hours = 1 nurse

Night shift: 258 minutes = 4.30 hours = 1 nurse

The required assistant nurse staffing per shift:

Morning shift: 465 minutes = 7.75 hours = 1-2 assistant nurses

Afternoon shift: 348 minutes = 5.80 hours = 1 assistant nurse

Night shift: 243 minutes = 4.05 hours = 1 assistant nurse.

Moreover, in the table we can observe below the following: the minutes and the hours they a nurse and an assistant nurse devote to every category of patients so as to deduce how many hours in total are needed to take care of 20 patients.

DISCUSSION

When the economic management in the health

	TIME IN MINS /24HOURS/ 20 PATIENTS		TOTAL TIME 24HOURS (MINS)	TOTAL TIME 24HOURS (HOURS)
LEVELS	NURSE	ASSISTANT NURSE		
LEVEL I (11PATIENTS)	22	26	528mins	8,8 h
LEVEL II (5 PATIENTS)	64	73	685mins	11,4 h
LEVEL III (3 PATIENTS)	82	86	504mins	8,4 h
LEVEL IV (1 PATIENT)	102	146	248mins	4,1 h
TOTAL:	1.574mins (26,23h)	1.056mins (17,6h)	2.630mins	43,8 h

care field are becoming more like those in the market for goods and services it is important that the patients' need for nursing care as well as the respective costs for the nursing care is documented in a systematic and reliable way. One way of doing so is to use a patient classification system. The patient classification system can be defined as a system that helps in grouping patients according to some observations or implied attributes or characteristics into homogeneous or mutually exclusive groups.[3] The patient classification system is a method of calculating nurse staffing. According to the American Nurses Association, adequate staffing should be reflected by analysis based on individual and aggregate patient needs. Also, specific patient needs should determine not only the number, but also the clinical skills (competencies) of nurses who will provide care.

There are organizations focusing on teaching how to develop and use patient classification systems such as "Patient Classification Systems International" (PCSI).[4] In 1985 Fries and Cooney held a survey of 1,469 patients to establish a classification system of long-term care patients.[2] In Sweden, a patient classification system, called the Zebra system, was developed.[5] The Zebra system makes it possible to both describe the individual patients' dependency level and to calculate the patients' requirements of nursing care in both staffing terms and costs, per month, per year, per patient stay, per diagnosis or DRG (Diagnosis-Related Group). It gives possibilities for managers to analyze the patient distribution in different categories of care during different periods of time, or if the patients' need of nursing care can explain the staffing requirements during a certain period, or if the distribution of days in different categories of care are related to age groups or diagnosis or DRG.[1]

The patient classification system is the method used to accurately calculate the staff needed. With this method, we can maximize the capabilities for efficiency and effectiveness of a department. In this way, we can administrate an organization and achieve economic benefits since we have the right number of resources to achieve the organization's goals. In the recent past, there have been several references to the patient classification system. Louet-Lehtoniemi studied nursing interventions in a neurosurgical operating room location, where she recorded and later categorized nursing procedures.[3] The classification of interventions in neurosurgical nursing into subcategories in accordance with the Oulu Patient Classification System has been use used as an aid in nursing decision-making and documentation in the observation room. In anaesthesiology, classification of patients according the degree of dependence

on nursing care and illness severity in a post-anesthesia care unit.[6] In Arizona, there have been commercial efforts towards implementation of patient classification systems for assessment of the optimal match of staffing personnel.[8] Within Greece, patients classifications systems have been developed in Intensive Care Units by investiging the correlation of APACHE II weighting patients index and nursing work severity index TISS – 28[9] and by comparison of disease severity indicators.[3] Others have studied the patient classification system in staffing and organization of nursing care in cardiac intensive care units in Greece.[10] In textbooks of management of health and nursing services, authors frequently refer to these patient classification systems.[11,12]

In the present study, we assessed the need for nursing staff per shift in a specific surgical oncology department with the description of nursing interventions and procedures and measurement of time using a patient classification system. The method appeared feasible in the clinical setting of a surgical oncology ward. The outcome was quite similar to the current practice. The results demonstrate the utility of the investigation at an administrative level.

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CASE REPORT

Small bowel metastasis of cutaneous melanoma as a cause of anaemia

E. de Bree,[1] M. Tzardi,[2] D. Michelakis,[1] K. Kalbakis,[3] O. Zoras[1]

[1]Department of Surgical Oncology, [2]Department of Pathology and [3]Department of Medical Oncology, Medical School of Crete University Hospital, Heraklion, Greece

ABSTRACT

Melanoma metastases to the gastrointestinal tract are relatively frequent, but rarely symptomatic. They may occur after a very long disease free interval, while highly unlikely in most tumours, bowel metastases should always be considered in the differential diagnosis of patients with a previous history of cutaneous malignant melanoma presenting with gastrointestinal symptoms such as anaemia, haemorrhage, obstruction and abdominal pain. Herein, a case of a 69-year old female patient presenting with anaemia twelve years after initial excision of a cutaneous melanoma is presented. The anaemia was caused by chronic haemorrhage which caused a small bowel metastasis. The management of gastrointestinal melanoma metastases is discussed. Surgical resection is the mainstay of treatment for acute complications of cutaneous melanoma which has metastasized to the bowel, with reported prognostic benefits in selected cases with limited extent of disease. However, whether bowel resection is indicated in asymptomatic metastatic disease remains controversial and this topic is further discussed. The optimal approach to resectable distant recurrent melanoma will likely be a combination of surgery and novel systemic therapies. An important challenge is in determining the optimal combination and sequence of these therapies for each patient.

KEY WORDS: melanoma, small bowel metastasis, surgery, anaemia

INTRODUCTION

Melanoma is the most common tumour to metastasise to the gastrointestinal tract, representing approximately one-third of all metastatic lesions to the gastrointestinal tract.[1] These tumours are commonly metastases from a cutaneous or less frequently, an ocular primary lesion. Rarely can malignant melanomas of the gastrointestinal tract be primary tumours. Although the likelihood of gastrointestinal metastases is higher for thicker melanomas, subsequent occurrence of bowel metastasis has even been reported in a patient with, initially, a localized thin melanoma.[2] Up to 60% of patients with malignant melanoma will have evidence of gastrointestinal metastases at autopsy, yet only 1-5% of all patients with malignant melanoma will have clinical manifestations of gastrointestinal tract involvement during their

Corresponding author
Eelco de Bree, MD, Department of Surgical Oncology, University Hospital, P.O. Box 1352, 71110 Heraklion, Greece, Tel.: +30-2810-392056 / 392382, Fax: +30-2810-392382, e-mail: debree@edu.uoc.gr

lifetime.[3-6] Acute presentations are intestinal obstruction (including intussusception), massive gastrointestinal haemorrhage and less commonly, perforation. Subacute presentation commonly includes symptoms of anaemia (including occult GI haemorrhage), cramping/chronic abdominal pain and an abdominal mass.[2,6-14]

Herein, a case of a melanoma patient with small bowel recurrence presenting with anaemia is described and the management of gastrointestinal melanoma metastases is discussed.

CASE REPORT

A 57-year old female patient was diagnosed with melanoma of the left shank. Diagnostic excisional biopsy had revealed an ulcerating nodular melanoma, with a Breslow thickness of 3.5 mm, a Clark level of invasion III, 49 mitoses per mm^2 and tumour free surgical margins. Subsequently she underwent wide local re-excision and biopsy of an ipsilateral femoral sentinel lymph node. Histological examination demonstrated no residual disease and absence of sentinel lymph node infiltration. No adjuvant treatment was administered. During follow-up examination there had been no sign of disease recurrence. Ten years after the initial diagnosis, she presented with a single nodular lesion of the left thigh. At physical examination there were no signs of local recurrence or other suspicious lesions on the left limb or the rest of the body. Imaging studies did not show systemic disease. Excisional biopsy of the lesion revealed an in-transit melanoma metastasis. Again adjuvant treatment was not administered.

Twelve years after the initial diagnosis, she presented with enlarged inguinal lymph nodes. Fine needle aspiration and cytological examination confirmed the presence of lymph node metastases. Imaging studies were negative for systemic disease. She underwent ilio-inguinal lymph node dissection. Her postoperative course was marked by wound infection and wound breakdown. Histological examination demonstrated gross malignant infiltration of one lymph node. The remaining 26 lymph nodes were free of metastatic tumour cells. Six months later, she presented with fatigue and weakness. Blood examination revealed significant anaemia (Hb 7.3 g/dL). Gastroscopy and colonoscopy did not show pathology. Computed tomography of the abdomen demonstrated a malignant asymmetric mass of an ileum loop over a length of 6 cm, with stenosis of the bowel lumen and an enlarged mesenteric lymph node (Figure 1), while computed tomography of the

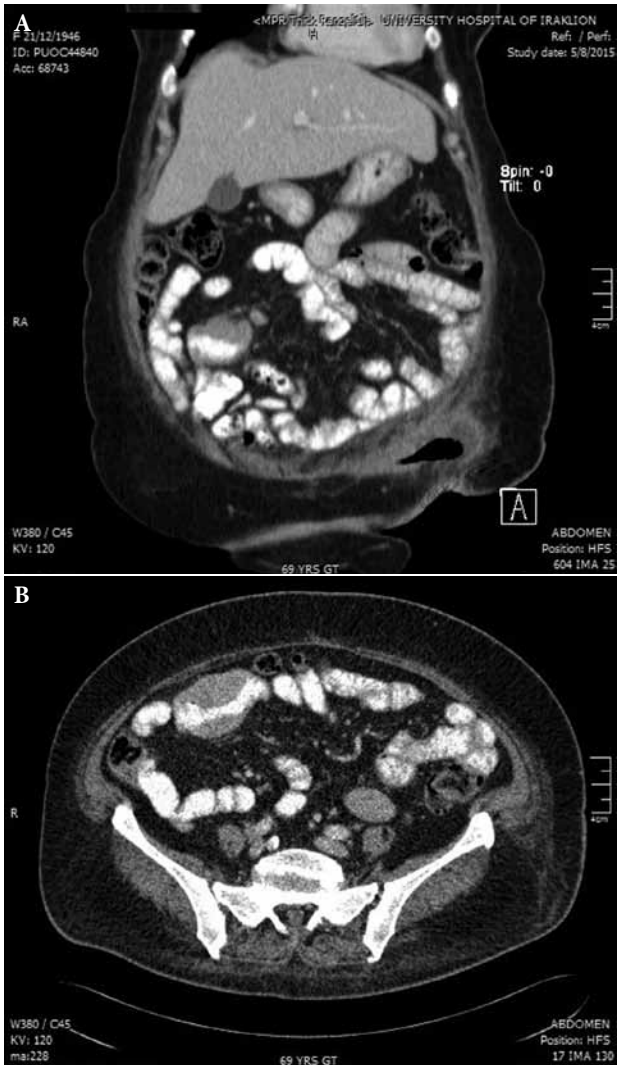

Figure 1. Computed tomography of the abdomen demonstrated a malignant asymmetric mass of an ileum loop over a length of 6 cm, with stenosis of the bowel lumen and an enlarged mesenteric lymph node.

chest revealed multiple nodular lung lesions and a mediastinal lymph node mass with a maximal diameter of 4.5 cm. Computed tomography of the brain demonstrated multiple brain metastases with a maximal diameter of up to 2.2 cm. Bone scan was without pathology. Because the most probable chronic blood loss originated from a small bowel metastasis, she underwent a palliative small bowel resection (Figure 2). Her postoperative course was uneventful. Histological examination confirmed the existence of a small bowel melanoma metastasis (Figure 3). The metastasis was 5 cm in maximal diameter and demonstrated full thickness invasion of the bowel wall, ulceration of the mucosa and infiltration of one of the five removed mesenteric lymph nodes. For her yet asymptomatic brain metastases, she underwent whole brain radiotherapy (20Gy, 5x4Gy). A B-Raf mutation was detected. Since her metastatic disease was asymptomatic, a fast short response was not necessary, but a more durable one was warranted. Consequently, she started systemic immunotherapy with ipilumimab, while the administration of a B-Raf enzyme inhibitor was reserved for eventual second-line treatment for progressive disease.

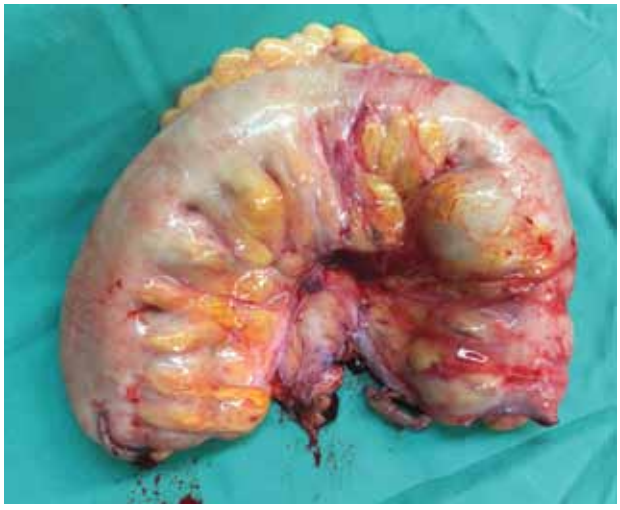

Figure 2. Specimen of the segmental small bowel resection for melanoma metastasis.

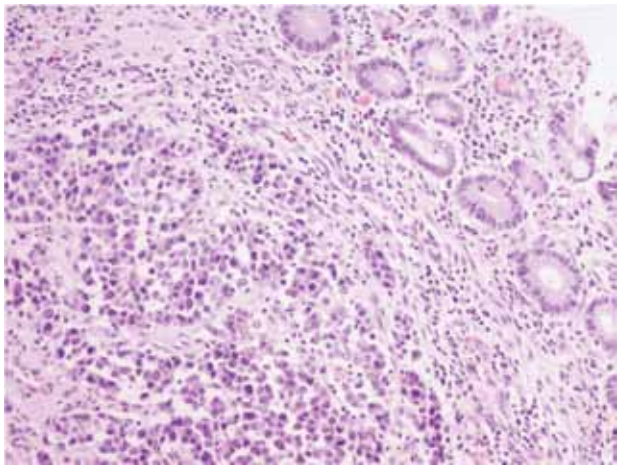

Figure 3. Histological examination demonstrated melanoma metastasis in the small bowel.

DISCUSSION

The reported post-mortem incidence of gastrointestinal metastases is 0.9% in 1000 melanoma patients.[1] In large autopsy series,[3-6] the small bowel was the most common (50–58%) site of gastrointestinal metastasis in melanoma patients. This prevalence showed an increase in patients with known distant metastases.[3-6] Despite the high prevalence, the majority of patients remain asymptomatic and only 1–5% of those with small intestine metastases develop clinically apparent symptoms.[5,14] In the majority of cases (52-90%), the gastrointestinal tract is involved at multiple sites. The jejunum and ileum are the most commonl(34-80%) harbour for metastases, followed by the colon (16-49%), duodenum (5-21%) and stomach (3-10%).[12] In the majority of cases, metastases other than gastrointestinal ones are detected at the time of surgery for gastrointestinal melanoma metastases.[10] Melanoma gastrointestinal metastasis is a late manifestation of the disease, with an overall dismal prognosis (5-year survival: 9-27%).[1,10-13,15] The reported median time between the diagnosis of melanoma and clinical detection of such metastasis is approximately 3 to 6 years.[10,15-19] In our patient, more than twelve years passed from the time of the initial diagnosis of cutaneous melanoma. A trend towards increased

time to gastrointestinal metastases with early stage primary disease has been reported.[10] In general, younger patients appear to present earlier with melanoma gastrointestinal metastases, while in older patients the metastatic behaviour of melanoma is usually indolent.

The most common presenting symptoms are anaemia (13-60%), abdominal pain (25-62%), gastrointestinal haemorrhage (26-44%), obstruction (18-27%), palpable mass (12%) and weight loss (9%).[6,7,10-13] The diagnosis may also be established when an emergency complication occurs, such as intestinal perforation, obstruction, intussusception and acute gastrointestinal bleeding.[6,10-13] The gastrointestinal tract is the first site of disease in 10-20% of patients with bowel resection for primary or metastatic melanoma.[10,15]

Melanoma patients with anaemia or evident gastrointestinal haemorrhage should initially, like any other patient, undergo upper gastrointestinal endoscopy and colonoscopy to determine the cause of blood loss. When endoscopy is inconclusive, the contrast-enhanced abdominal computed tomography should be performed, although its sensitivity in diagnosing small bowel metastases is only 66%.[16] The diagnostic value of positron imaging tomography in diagnosing visceral melanoma metastases is superior,[20-22] but unfortunately this imaging modality is not available everywhere. In our geographical region, there is still no access to positron imaging tomography. In the case that the above diagnostic examinations have been negative, the use of capsule endoscopy has been recommended.[23,24] In our case, the computed tomography demonstrated the small bowel metastasis, which caused anaemia, as well as multiple brain metastases.

In the case of complications such as haemorrhage, perforation and obstruction, it seems clear that bowel metastases are managed by segmental bowel resection, even in the presence of other irresectable distant disease. In our patient, resection of small bowel metastasis was indicated because of the haemorrhage, despite the multiple brain metastases. Subsequently, she received whole brain radiation for her asymptomatic multiple brain metastases and systemic treatment with ipilumimab. However, whether bowel resection is indicated in asymptomatic metastatic disease remains controversial. Many medical oncologists believe that once melanoma has spread through the bloodstream to a distant site, surgery is not useful because patients already have clinically relevant circulating tumour cells and subclinical occult metastases. Thus, they consider systemic medical therapy the mainstay of management for distant metastases.[25,26] However, in the case of a limited number of distant metastases, also called oligometastatic disease, surgery may be indicated. In the past, several studies suggested that surgical resection of distant melanoma metastases should be undertaken whenever surgical removal of all macroscopic metastatic disease is feasible.[1,12,13,27-33] Resection of intra-abdominal melanoma metastases had been associated with improved survival, irrespective of the number of metastatic sites. Retrospective analysis of the data of the large MSLT-I trial,[34] patients with non-lung visceral metastases (stage M1c) who underwent surgery, with or without accompanying medical therapy, had a 15.0-month median survival compared with 6.3 months for those treated with systemic therapy alone ($p<0.0001$). Promising data from recent trials of novel immunotherapy and targeted therapy[35-43] challenge the above results which were obtained in an era with systemic treatment of limited effectiveness. On the other hand, surgery for gastrointestinal metastases is an effective treatment that is associated with low morbidity and provides high symptom control. In conclusion, there is currently no standard approach to treatment of distant melanoma or consensus on the role of surgery. The adequate selection of patients who may benefit from surgery for gastrointestinal metastases is of outmost importance. Patients who are not likely to recur early after resection, who do not have prior lymph node metastases, who have no extra-gastrointestinal

metastases, whose metastatic disease is completely resectable, who present after a longer interval (≥12 months) from treatment of the primary melanoma, a low serum LDH level and who do not have more than two organs involved seem to be the best candidates.[10,12,34] The optimal approach to resectable distant recurrent melanoma will likely be a combination of surgery and systemic therapies. As novel targeted agents continue to demonstrate encouraging results in trials,[35-43] more patients will become candidates for neoadjuvant or postoperative systemic treatment regimens. Indeed, many of the new systemic agents can demonstrate reduced disease progression but do not yet create high complete response rates, thus suggesting a role for surgery. An important challenge is in determining the optimal combination and sequence of these therapies for each patient.

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CASE REPORT

Skin necrosis following injection of patent blue V dye for sentinel lymph node biopsy
Report of a case and literature review

A. Karavelia, D. Stamatiou, J. Askoxylakis, E. de Bree, O. Zoras

Department of Surgical Oncology, Medical School of Crete University Hospital, Heraklion, Greece

ABSTRACT

Lymphatic mapping in the context of sentinel lymph node biopsy (SLNB) is a minimally invasive procedure that allows for accurate staging of the axilla in patients with breast cancer. Either radiocolloid, blue dye, or their combination, can be used. We present a rare case of skin necrosis at the site of subareolar injection of patent blue V for SLNB in a post-menopausal patient with breast cancer. After excision of the necrotic area and primary wound closure, a good cosmetic outcome was achieved. Although adverse events following the use of patent blue V dye are not common, the possibility of potential skin necrosis should be kept in mind.

KEY WORDS: breast cancer, sentinel lymph node biopsy, blue dye, patent blue V, skin necrosis

INTRODUCTION

Lymphatic mapping and sentinel lymph node biopsy is a minimally invasive technique, first described by Guiliano et al,[1] that provides accurate nodal staging, with associated minimal morbidity.[2] Nodal staging is of significance in breast cancer patients since the lymph node status is an important prognostic factor and an indicator for adjuvant systemic treatment.

Sentinel lymph node identification can be achieved using either a blue dye (isosulphan blue or patent blue V), a radiocolloid (Tc99-sulphur colloid), or their combination.[3] While all three techniques have been reported to be reliable in experienced hands, the combined technique appears to have a higher success rate and lower false negative rate compared to either technique on its own.[3] In the past, the radiotracer and/or blue dye were injected either intratumorally or peritumorally. More recent studies suggest intradermal, subdermal and subareolar injection.[3]

Herein, we present a rare case of skin necrosis after subareolar injection of patent blue V dye in a woman with breast cancer, who underwent sentinel lymph node biopsy and review the associated literature.

Corresponding author
D. Stamatiou, MD, PhD, Department of Surgical Oncology, University Hospital, P.O. Box 1352, 711 10 Heraklion, Crete, Greece, Tel.: +30-2810-392382, Fax: +30-2810-392382, e-mail: jpstamatiou@yahoo.gr

CASE REPORT

A 70-year-old post-menopausal woman was referred to our department for surgical management of breast and colon cancer. Her medical history included diabetes and arterial hypertension. Initially, she presented with a 4 cm lump in her right breast, while there were no palpable lymph nodes in the axilla. Mammography and ultrasonography demonstrated a highly suspicious lesion in the inner upper quadrant of the right breast. Tru-cut biopsy confirmed the diagnosis of an invasive lobular carcinoma. Disease staging imaging was negative for metastatic disease, but on abdominal computed tomography an incidental mass of the ascending colon was found. The patient received 8 cycles of neoadjuvant chemotherapy, which included four cycles of combination of fluorouracil, epirubicin and cyclophosphamide (FEC), and an additional four cycles of docetaxe-, as the breast tumor was considered locally advanced (4 cm in diameter, clinically T2 N0). In the meantime, she underwent colonoscopy for investigation of the lesion of the ascending colon. Endoscopic biopsy of the tumor revealed a colon adenocarcinoma. The patient underwent quadrantectomy and sentinel lymph node biopsy with the use of subareolarly injected patent blue V dye, followed by laparoscopic right colectomy. No adverse effects or intraoperative systemic allergic reactions were noted. Since the sentinel node was found to be infiltrated at frozen section histology, completion axillary lymph node dissection was performed.

Histological examination of the breast and axilla revealed a grade 2 tubulolobular breast adenocarcinoma of 4 cm and 3 involved lymph nodes out of 15 (pT2N1). Immunohistochemical examination demonstrated: PR Allred score 5, ER Allred score 8, HER-2 score 0, ki67 5% and no p53 mutations. Histological examination of the right colectomy specimen revealed a moderate differentiated adenocarcinoma of the colon with serosal invasion and 2 out of 19 lymph nodes with metastatic disease (T3N1, Duke C).

The patient made an uneventful recovery. Following the principles of fast-track surgery, she was discharged from the hospital on the seventh postoperative day, after she had received solid food and had normal bowel movements. Neither the quadrantectomy nor the axillary incision showed signs of infection, while the blue pigmentation of the periareolar skin remained postoperatively.

When the patient was seen in the outpatient clinic, approximately one month postoperatively, ulceration at the site of the former injection of the blue dye was noted (Figures 1a and 1b). Skin biopsy of the ulceration area revealed necrosis of the skin and necrosis of fibrous tissue and dermis. The whole necrotic area was excised and the wound was closed primarily, with non-absorbable stitches, achieving a good cosmetic outcome.

The patient received breast radiotherapy followed by adjuvant chemotherapy for colon cancer (capecitabine plus oxaliplatin). On completing her second chemotherapy schedue, she started

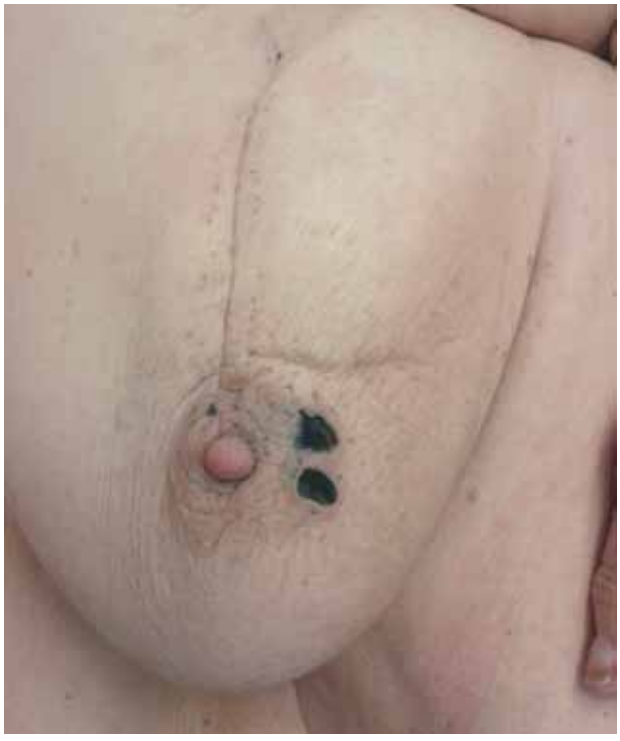

Figure 1a. Postoperative necrosis at the site of dye injection.

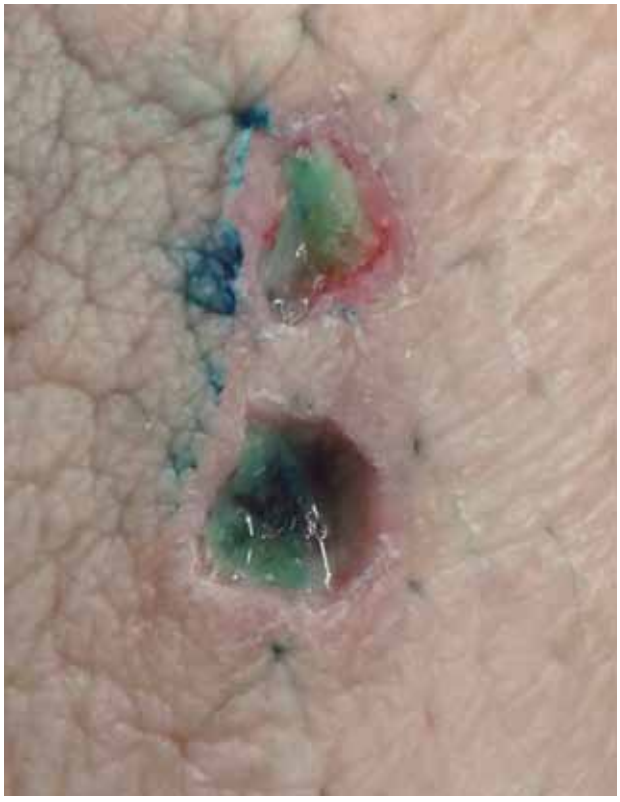

Figure 1b. Necrotic area in detail.

adjuvant hormonal therapy for her breast cancer with an aromatase inhibitor (letrozole). On recent follow-up examination, 18 months postoperatively, she was in good condition and free of disease.

DISCUSSION

On axillary assessment with the sentinel lymph node biopsy, using the blue dye technique, three different dyes have been used: 1) patent blue V, 2) isosulphan blue, a 2,5-disulfonated isomer of patent blue, and 3) methylene blue (methylthioninium chloride).[4] Isosulphan blue is the dye that has been traditionally used in sentinel lymph node biopsy.[5] However, a number of allergic reactions, some of which have proved to be life threatening, have discouraged its use in breast cancer patients.[6] Methylene blue represents a safer substitute, with fewer allergic reactions, yet, its application has been related to local as well as systemic complications such as adverse skin reactions,[7] skins eruptions and rashes,[8] subcutaneous tissue necrosis,[9] abscess formation,[9] and even capsular contraction after breast reconstruction using an implant, with the prosthesis exhibiting intense blue discoloration, with intense blue discoloration of the prosthesis.[10] Patent blue V injection, has been associated with minor local complications, such as long-term skin discoloration at the injection site.[11] However, anaphylactic shock has been reported following its injection,[12,13] the risk of which can be reduced by corticosteroid and antihistamine use.[6,14,15]

This is the second case of skin necrosis following injection of patent blue V dye for SLNB. The other case referred to a 51-year-old postmenopausal woman, who underwent SLNB, skin sparing mastectomy, as well as immediate reconstruction using a latissimus dorsi musculocutaneous flap.[4] That patient had also undergone intradermal injection of radiocolloid the day before surgery, while skin necrosis was noticed on the 9th postoperative day.[4] No radiocolloid was used in our patient, and skin necrosis was observed about a month postoperatively. In contrast to the patient of the other case report, our patient suffered from diabetes, which may predispose to periareolar skin microangiopathy, and offer a potential explanation for local dermal necrosis. A case similar to ours, but with intradermal injection of methylene blue, has also been reported.[5]

In conclusion, patent blue has a relatively favorable side-effect profile compared to the other two dyes used in sentinel lymph node dissection for breast cancer; therefore, its use is strongly recommended.[4,5] Although rare, the possibility of dermal necrosis postoperatively, should be kept in mind. Should it occur, a good cosmetic outcome can be achieved with surgical excision of necrotic tissue and primary closure, provided the necrotic area is relatively small.

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