QUARTERLY PUBLICATION OF THE HELLENIC SOCIETY OF SURGICAL ONCOLOGY

Hellenic Surgical Oncology

May-August 2014 – VOLUME 5 – NUMBER 2

Ελληνική Χειρουργική Ογκολογία

ΕΛΛΗΝΙΚΗ ΧΕΙΡΟΥΡΓΙΚΗ ΟΓΚΟΛΟΓΙΑ
Ιδιοκτήτης: ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΧΕΙΡΟΥΡΓΙΚΗΣ ΟΓΚΟΛΟΓΙΑΣ

ΕΚΔΟΤΗΣ – ΔΙΕΥΘΥΝΤΗΣ:
Ι. Σπηλιώτης

ΕΡΓΑΣΙΕΣ-ΣΥΝΔΡΟΜΕΣ ΜΕΛΩΝ-ΑΛΛΗΛΟΓΡΑΦΙΑ:
ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΧΕΙΡΟΥΡΓΙΚΗΣ ΟΓΚΟΛΟΓΙΑΣ
Σεβαστουπόλεως 76 – 115 26 Αθήνα
Τηλ.: 210 69 82 950, Fax: 210 6994258,
e-mail: eis-iatriki@otenet.gr

ΕΤΗΣΙΕΣ ΣΥΝΔΡΟΜΕΣ: 50 €

ΒΙΒΛΙΟΘΗΚΕΣ-ΟΡΓΑΝΙΣΜΟΙ-ΙΔΡΥΜΑΤΑ: 100 €

ΕΚΔΟΣΕΙΣ: ΤΕΧΝΟΓΡΑΜΜΑ*med*
Λ. Μεσογείων 380 – 153 41 Αγ. Παρασκευή
Τηλ.: 210 60 00 643, Fax: 210 6002295
e-mail: techn@hol.gr

Hellenic Surgical Oncology

HELLENIC SURGICAL ONCOLOGY
OFFICIAL PUBLICATION OF THE HELLENIC SOCIETY OF SURGICAL ONCOLOGY

PUBLISHER – DIRECTOR:
J. Spiliotis

PAPERS' SUBMISSION-FEES PAYMENT-CORRESPONDENCE:
HELLENIC SOCIETY OF SURGICAL ONCOLOGY
76 Sevastoupoleos street – GR-115 26 Athens
Tel.: +30 210 69 82 950, Fax: +30 210 6994258,
e-mail: eis-iatriki@otenet.gr

ANNUAL SUBSCRIPTIONS: 50 €

LIBRARIES-ORGANIZATIONS-INSTITUTIONS: 100 €

PUBLISHING: TECHNOGRAMMA*med*
380 Mesogeion Ave. – GR-153 41 Agia Paraskevi
Tel.: +30 210 60 00 643, Fax: +30 210 6002295
e-mail: techn@hol.gr

Hellenic
Surgical
Oncology

QUARTERLY PUBLICATION OF THE HELLENIC SOCIETY OF SURGICAL ONCOLOGY

CONTENTS

Editorial

Dear Colleagues,

It is an honour that the position of Editor-in-Chief was assigned to me by the new Board of Directors of the Hellenic Society of Surgical Oncology in March 2014. On behalf of all the members of the Editorial Board, I would like to thank the Board of Directors for giving us the opportunity to work for this Journal. As the President of the Society has already stressed in the Preface of the Journal's previous issue, one of the goals of the New Board of Directors is to work towards the indexing of the journal in Medline. Bearing in mind the infancy of our Journal, this seems quite a challenging task and one which requires effort from all of us.

Due to the more demanding and international character of the Journal to which we aspire, a new Editorial Board will be formed. The new Editorial Board will consist not only of experienced scientists and clinicians in the field of Surgical Oncology in Greece, but also of worldwide leading physicians beyond Greece. The editorial team members are expected to offer new ideas to render the Journal more attractive and scientifically competitive. Our goal is to broaden the excellent work done by the former editorial team by increasing the Journal's international profile, while providing readers with an even more interesting and interdisciplinary content. I am confident that all the members of the new Editorial Board will work eagerly in order to improve our Journal.

The inclusion criteria of the Literature Selection Technical Review Committee for inclusion of the Journal in Medline are not easy to meet. The criteria have as critical elements the quality of the content, the quality of the editorial work, and the quality of the production. Regarding the latter, I would like to thank our publisher TECHNOGRAMMAmed for their unwavering and much appreciated high quality support over the past years. Recently, a sponsor was found to cover the publishing expenses and to ensure the quality of production in exchange for advertisement placements. The next two parameters require great effort from all of us. Firstly, we need submission of a sufficient number of manuscripts. The Editorial Board would like to encourage you all strongly to write and submit any manuscript of adequate quality in the field of Surgical Oncology. Such a manuscript may include review articles, original articles concerning clinical, experimental and/or research studies, case reports, discussions of controversial issues, reports of seminars, symposia, round table discussions and lectures, book reviews and letters to the Editor. To improve the quality of the papers that are to be published in the Journal, new Guidelines

*for Authors have been defined and published in the Journal. To contribute to the objectivity, credibility and quality of the Journal's content, a quick peer review process, with strict limits and monitoring, will be offered to all manuscripts submitted to the Journal. To further facilitate accessibility to the Journal, electronic appearance of the contents of each issue on the website of the Hellenic Society of Surgical Oncology (*www.eexo.gr*), which will be reconstructed in the near future, will be provided. Additional relevant improvements are also under way.*

Our aim is a high quality Journal which features superior clinical studies (from Greece and abroad), substantial observational data and interesting cases, discusses points of view and updates our readers on recent advances by publishing outstanding reviews and relevant breaking news in the various fields of Surgical Oncology.

All the Members of the new Editorial Board are well aware of the challenges posed by the ever increasing international competition in the sector of medical publications concurrent with the difficult period facing our country. However, over the next years we will work diligently to improve the Journal to one which carries a prestigious national and international reputation by publishing high quality papers and by being abstracted and indexed in the main journal databases. In order to succeed in these objectives, we look forward to receiving your high quality submissions, general feedback and suggestions for improving the Journal.

On behalf of the Editorial Board,

Eelco de Bree
Editor-in-Chief

HELLENIC SURGICAL ONCOLOGY 2014; 5(2): 58-73

REVIEW

Small bowel lymphoma: The surgeon's role

A. Leventi,[1] E. de Bree,[1] J. Grammatikakis,[2] M. Tzardi[3]

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

ABSTRACT

Although lymphoma in general is considered a disease treated by haematologists, there are some facts that surgeons should know about small bowel lymphomas as they may encounter such patients in emergent and elective settings. The choice of the optimal treatment may be challenging and depends mainly on the specific histological diagnosis. Herein, the literature is reviewed and the role of surgery in its management, which may become more limited in the near future with the introduction of novel diagnostic and therapeutic methods, is discussed.

Key words: Intestinal lymphoma, management, clinical presentation, surgery

INTRODUCTION

Small bowel malignancies are rare and account for 1-2% of all primary gastrointestinal malignant tumours.[1-3] Their prognosis and management is highly determined by their histological subtype, while their clinical presentation is variable and depends on the anatomic location of the primary tumour.

Among all small bowel tumours, lymphoma is the third most frequent, following adenocarcinoma and carcinoid tumours. Depending on race and gender, it constitutes of 7% to 23% of all small bowel tumours.[4] These lymphomas are generally non-Hodgkin lymphomas (NHL) and most frequently, marginal zone B-cell lymphomas of mucosa associated lymphoid tissue (MALT lymphomas). Although the incidence of MALT has been rising over the last years,[5] it still remains a rare disease found at variable sites along the small bowel. Due to its rarity and heterogeneity, there are no specific evidence-based guidelines for management of small bowel lymphoma in major surgical textbooks.

Although haematologists are more familiar with lymphomas and play a most fundamental role in their treatment, there are facts that a surgeon should know regarding small bowel lymphoma in order to determine his or her role in its management. Herein, we report an illustrative case in which diagnosis of small bowel lymphoma was suggested preoperatively and review the literature on its incidence, pathogenesis, diagnosis, classification, staging and management, while placing

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

emphasis on the surgeon's role. A literature search was undertaken and the most relevant data from the articles are included in this review.

CASE PRESENTATION

A 65-year old male presented in our hospital with repeating episodes of incomplete small bowel obstruction. He reported four self-limiting events of intermittent colicky abdominal pain and vomiting over the course of the preceding seven months. He had no history of previous abdominal surgery. On admission, physical examination was unremarkable. Laboratory examinations were all within normal range.

Plain abdominal radiographies in supine and upright position were normal. A computed tomography (CT) scan of the abdomen revealed thickening and dilation of the small bowel without abdominal lymphadenopathy or any other abnormalities (Figure 1). A magnetic resonance imaging (MRI) of the abdomen confirmed the CT findings, showing a thickening of the small bowel wall of 1.4 cm, over a length of 8 cm (Figure 2). Endoscopy of the upper gastrointestinal tract showed diffuse oedema and cherry red spots on the gastric wall from which the biopsy revealed chronic gastritis, while endoscopy of the rectum, colon and terminal ileum failed to demonstrate any pathology. After referral to our hospital, an enteroclysis was performed (Figure 3) which demonstrated thickening and disorganization of

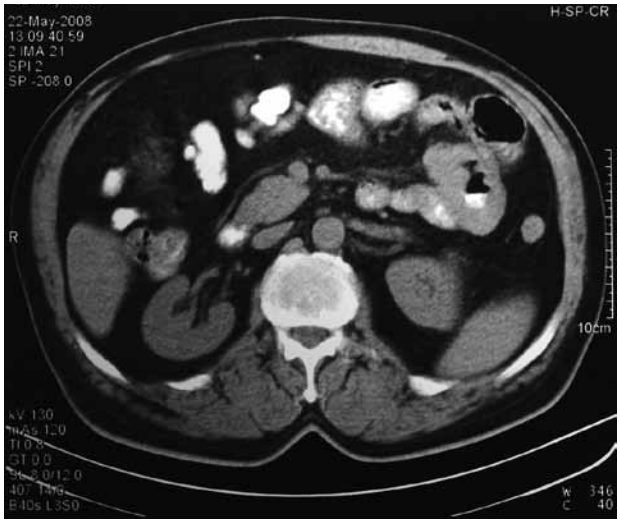

Figure 1. CT of the abdomen showing dilatation of a small bowel segment with thickening of its wall.

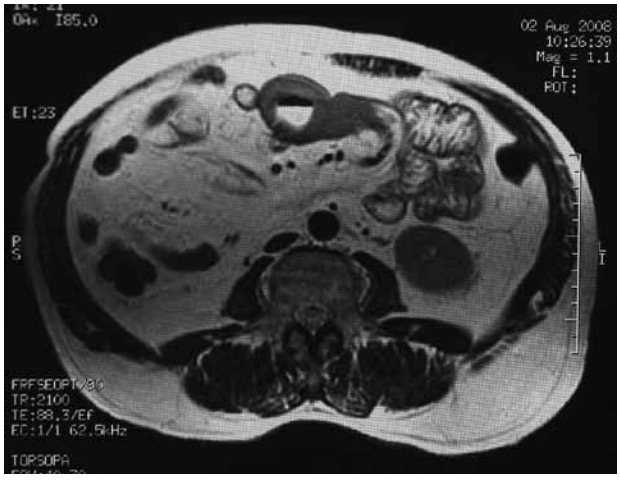

Figure 2. T2-weighed MRI showing thickening of the small bowel wall and adjacent mesentery.

Figure 3. Enteroclysis demonstrating thickening and disorganisation of circular bowel folds over a distance of approximately 10 cm.

the jejunal folds, at a distance of approximately 50 cm from the Treitz's ligament and over a total length of 10 cm. The radiological appearance was suggestive of a neoplasia of lymphogenous origin.

Because the lesion was considered inaccessible for conventional endoscopic biopsy, double-balloon endoscopy was not available and the patient had symptoms of bowel obstruction, a multidisciplinary team decided on a surgical approach. At laparotomy, a mass infiltrating the bowel wall with expansion to the adjacent mesentery (Figure 4) was found approximately 50 cm from the Treitz's ligament. A segmental resection of the small bowel along with the adjacent mesentery was performed and the continuity of the bowel was restored with an end-to-end anastomosis. The postoperative course was uneventful.

Histological examination revealed thickening of a small bowel segment and its mesenterium (Figure 5) caused by diffuse infiltration of neoplastic cells, small to medium in size, through the entire thickness of the bowel wall into the adjacent fatty tissue, with significant ulceration of the mucosa (Figure 6). Some nuclear polymorphism and rare mitoses were seen. Combined cell morphology and immunohistochemistry findings were supported the diagnosis of NHL consisting of small B cells of marginal zone origin (MALT lymphoma). The surgical margins of the small bowel were free of disease. Thirteen of the twenty-two removed mesenteric lymph nodes had been affected by this MALT lymphoma. Staging imaging with CT of the abdomen, neck and thorax was negative for further lymph node involvement. Bone marrow biopsy did not show infiltration by lymphoid cells. In conclusion, our patient had stage IIE disease according to the Musshof modification of the Ann Arbor staging system or pT3N1M0B0 small bowel lymphoma according to the Paris staging system (see the section 'Staging'). Postoperatively

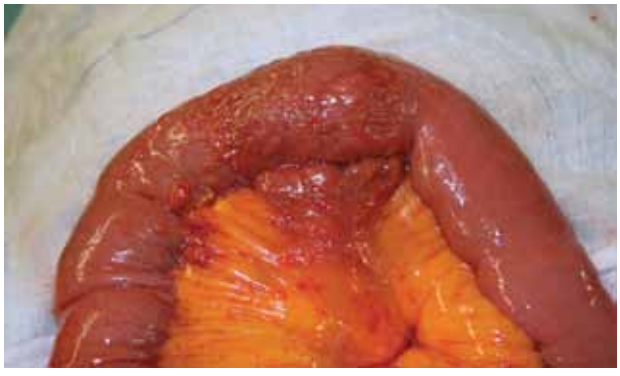

Figure 4. Intraoperative findings of thickened small bowel segment and mesentery.

Figure 5. Transection through the resected small bowel specimen, showing thickening of the bowel wall and of the adjacent mesentery.

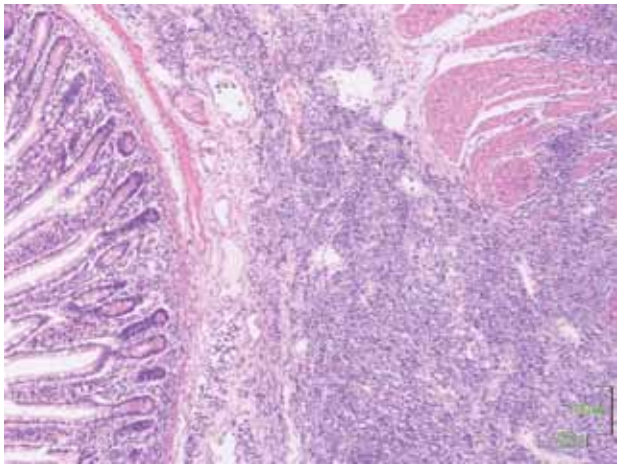

Figure 6. Microscopic examination of the resected small bowel demonstrated diffuse infiltration of neoplastic cells, small to medium in size, through the entire thickness of the bowel wall and into the adjacent fatty tissue, with significant ulceration of the mucosa. Some nuclear polymorphism and rare mitoses were seen.

he received six monthly cycles of chemotherapy with R-COP (rituximab 700 mg/m^2, cyclophosphamide 2 mg/m^2, vincristin 2mg/m^2, prezolon 75mg/m^2 for 5 days).

At follow-up examination one month after the completion of chemotherapy, a lesion in the stomach was detected during upper gastro-intestinal endoscopy. Histological examination of the biopsy demonstrated infiltration of the gastric mucosa by MALT lymphoma with a dominant plasmatocytic component. *Helicobacter pylori* was not detected. Subsequently, he received 12 additional monthly cycles of chemotherapy with chlorambucil 0.1 mg/kg. After the completion of the second line chemotherapy, imaging studies and endoscopy remained negative. Four years postoperatively, he is in good condition and free of disease.

Small bowel tumors and lymphoma

Despite the fact that the small intestine represents approximately 75% of the total length of the gastrointestinal tract and more than 90% of the mucosal surface, malignant tumours rarely occur there (1-2% of all gastrointestinal malignancies).[1-3] Many different histological types of benign and malignant small bowel tumours have been identified (Table 1). Primary extranodal lymphoma is one of the most commonly encountered.[1-3] Per anatomic subsite, small bowel lymphoma is, in total, most frequently observed in the ileum, but as a proportion of all small bowel malignancies, the highest percentage of lymphoma is observed in the jejunum, due to the increased incidence of ileal carcinoid. Lymphoma constitutes of 22% of the jejunal, 17% of the ileal and 10% of the duodenal malignant tumours.[4]

Table 1. Differential diagnosis of small bowel tumors[2].

Benign	Malignant
• Leiomyoma/Gastrointestinal stromal tumor (GIST) • Adenoma • Lipoma • Brunner's gland hamartoma • Hemangioma • Intestinal follicular metaplasia	• Metastatic from breast or lung cancer, or malignant melanoma • Adenocarcinoma • Lymphoma • Leiomyosarcoma • Neuroendocrine tumors

The definition of primary extranodal lymphoma, especially in the presence of both nodal and extranodal disease, remains controversial. Frequently, a lymphoma is considered to be primary extranodal, when after routine staging procedures there is either no, or only 'minor', nodal involvement, along with a clinically 'dominant' extranodal component to which primary treatment must be directed.[6] More specifically, criteria which have been proposed for the diagnosis of primary intestinal lymphoma include (1) absence of peripheral lymphadenopathy at the time of presentation, (2) lack of enlarged mediastinal lymph nodes, (3) normal total and differential blood cell count (4) predominance of bowel lesion at the time of diagnosis with only lymph nodes obviously affected in the immediate vicinity and (5) no lymphomatous involvement of liver or spleen.[7]

INCIDENCE OF SMALL BOWEL LYMPHOMA

Extranodal primary lymphomas most often appear in the gastrointestinal tract (40%), mainly localized in the stomach (30-60%) and small bowel (20-30%).[8,9] These small bowel lymphomas are typically NHLs and most commonly affect the ileum (50%), followed by the jejunum (30%) and the duodenum (20%).[4,9] They are more common in geographic localities such as the Middle East and North Africa.[8] Its incidence in the U.S.A. has been estimated to be 3.5 per 1,000,000 citizens per year and varied depending on race and gender. A higher incidence was seen among men and among black citizens.[4] As with many other extranodal lymphomas, their incidence has increased significantly in the last decades.[10] Changes in the epidemiology of human immunodeficiency virus (HIV) infection and other viral and microbial infections, immuno-

suppressive treatments, or environmental factors, including pesticides and solvents, might explain this trend, along with the increase attributed to improved diagnostic techniques.[6]

NORMAL LYMPHOID TISSUE OF THE SMALL BOWEL

To understand the pathogenesis and classification of small bowel lymphomas, one should know basic facts regarding the normal small bowel lymphoid tissue. The intestine is a site where antigenic stimulation occurs continuously. To fulfill its absorptive function, it has a huge surface area of 400 m^2, lined with specialized epithelium made of cells tightly connected to each other. It also has its own specialized lymphoid tissue consisting of lymphocytes and organized areas of lymphoid tissue in the mucosa. These areas are called Peyer's patches, and were first described by Peyer in 1687.[11] Such a patch consists of a central germinal centre with follicular B-cells, which participate in T-cell dependent immune responses, and a surrounding marginal zone (MZ) with a distinct subset of B-cells, the MZ B-cells. The majority of MALT lymphomas appear to originate from MZ lymphocytes. These cells, owing to their frequent auto reactive and cross-reactive action as well as their relative hyper-reactivity to activation, are found in various pathological conditions involving autoimmunity and infection.[12]

Furthermore, the intraepithelial lymphocytes reside in scattered formation among the surface epithelial cells of the small intestine. These T cells are distinct from both those of the follicle-associated epithelium and lamina propria and represent a heterogeneous population not only in their molecular phenotype, but also in their function.[13]

CLASSIFICATION, PATHOGENESIS AND GENERAL CHARACTERISTICS

Small bowel lymphomas are divided into several subtypes, according to the latest World Health Organization (WHO) classification and assessed by morphological, molecular, biological, aetiopathogenetical and biological features (Table 2).[14] This classification has prognostic and therapeutic implications and therefore it is important to establish the exact histological type of the lymphoma accurately. Primary small intestine lymphomas are much more heterogeneous than those in the stomach. Most frequently, a B-cell lymphoma is diagnosed (in 90% of cases, as in the case of our patient) while a T-cell lymphoma or Hodgkin lymphoma is rare.[9,15] B-cell lymphomas of low grade are of the MALT type and usually have a more indolent course. Contrarily, other lymphomas, especially high-grade diffuse large B-cell lymphomas, have a more aggressive biological behaviour. The most frequent types are discussed below.

Table 2. Classification of primary lymphomas of the small bowel according to the WHO classification.[13]

B cell
Extranodal marginal zone B-cell
• 'Western-type' MALT lymphoma (focalized)
• 'Mediterranean type' MALT lymphoma (extensive)
• IPSID (essentially alpha-chain disease)
Mantle zone lymphoma
Burkitt lymphoma
Diffuse large B-cell lymphoma
Follicular lymphoma
Other rare types (small lymphocytic and lymphoplasmaticytic lymphoma, plasmacytoma)
T cell and NK cell
T-cell associated with enteropathy (EATL)
Others rare types (adult T-cell lymphoma, nasal-type T/NK-cell lymphoma)
Hodgkin lymphoma
Others

MALT: Mucosa Associated Lymphoid Tissue; IPSID: Immunoproliferative Small – Intestinal Disease; NK: natural killer; EATL: Enteropathy Associated T-cell Lymphoma.

MALT lymphoma

Extranodal MALT lymphomas arise in gastrointestinal sites such as the stomach, the intestine or the gallbladder, and non gastrointestinal sites such as the salivary glands, conjuctiva, thyroid, orbit, lung, breast, kidney, skin, liver, and prostate.[16] Many of these sites are normally deprived of any organized lymphoid tissue and lymphoma arises there from MALT as a result of chronic inflammatory stimulation. The disease is associated with specific types of microbial infection, with the best known being the relation of gastric lymphoma with Helicobacter Pylori infection of the stomach[5,17] and with autoimmune disorders such as Hashimoto thyroiditis and Sjögren syndrome. The auto reactive lymphoid tissue that is accumulated under inflammatory stimulation becomes genetically unstable with the acquisition of abnormalities such as translocation t(11;18) and t1;14 trisomy 3, c-myc (8q24) and p53 (17p13) mutations leading to transformation into MALT lymphoma.[16]

Although MALT lymphoma was classically considered a localized disease which remains confined to the site of origin for a prolonged period after diagnosis,[18] there is increasing evidence of disseminate disease at presentation[16,19-21] or during follow up.[22-24] The tendency of MALT lymphomas to metastasize to another site within the organ of origin, or to another MALT-containing organ, is unique among the lymphomas and has been described by Isaacson as 'the MALT concept'.[25] Dissemination inside the organ of origin and inside MALT containing organs may be biologically linked to the expression of special homing receptors or adhesion molecules at the surface of MALT normal and lymphoma cells.[26] Especially in the case of concurrent gastric and intestinal MALT lymphoma, there is evidence that both are derived from the same tumour clone, suggesting that the intestinal lesions result from dissemination of gastric tumours or vice versa.[27] The latter was also observed in the present case.

Mantle cell lymphoma

Mantle cell lymphoma is another subtype of B-cell NHL which usually affects individuals over 50 years of age. Intestinal mantle cell lymphoma usually involves the terminal ileum and ileocecal valve, appearing typically as numerous polyps, hence also called multiple lympomatous polyposis. The early stages of primary small bowel mantle cell lymphoma may present as an ulcerated or nodular mass in the terminal ileum, suggestive of Crohn's disease. It is characterized by the chromosomal translocation t(11:14), resulting in overexpressing of cyclin-D1. Cyclin-D1 is a nuclear protein that promotes cell proliferation. Positive immunohistochemical staining for this protein is diagnostic for mantle cell lymphoma. Differentiating mantle cell lymphoma from follicular and MALT lymphoma is essential for determining of the therapeutic approach.[13,28]

Burkitt lymphoma

Burkitt lymphoma, which is most common in children and young adults, usually involves the terminal ileum with extensive abdominal involvement. The endemic form typically occurs in equatorial Africa and New Guinea, while the sporadic form appears worldwide.[13] It usually presents with abdominal pain, bleeding and bowel obstruction, often caused by intussusceptions. Its aetiology is associated with Epstein Barr virus (EBV) and HIV.[9,29] Burkitt lymphoma is thought to arise in the context of lymphatic hyperplasia with polyclonal B-cell expansion in response to malaria and HIV, respectively. The uncontrolled proliferation of EBV-positive B-cells in turn introduces genetic instability, which increases the risk of c-myc rearrangement and, ultimately, lymphoma. However, only approximately one third of Burkitt lymphomas appear to be associated with EBV and its pathogenesis remains poorly understood.[13]

Diffuse large B-cell lymphoma

This type is the most common lymphoma af-

fecting the small bowel and may occur *de novo* as a primary process or arise secondary to progression or transformation of a more indolent lymphoma, for example, follicular lymphoma or MALT lymphoma. Therefore, this term probably encompasses a heterogeneous population. These tumours may be relatively large and ulcerate. Cases occurring in the context of immunosuppression tend to have a higher incidence of EBV positivity, while cases arising from MALT lymphoma are t(11;18) negative, in contrast to the true MALT lymphoma which is often t(11;18) positive. The neoplastic B-cells express CD19, CD20, CD22 and CD79a. Diffuse large B-cell lymphoma that is transformed from MALT tends to be negative for bcl-2 and CD10, while contrarily, primary gastrointestinal diffuse large B-cell lymphoma may be positive for these markers.[13]

Immunoproliferative small intestine disease

Another type, immunoproliferative small intestine disease (IPSID) or α-chain disease, mainly affects older children and young adults, predominately in the proximal small bowel, and is usually associated with chronic diarrhoea and abdominal pain. This type is most frequently seen in the Middle East and countries such as India, but also in the Far East, developing Mediterranean countries and North and South America.[13,29] Sporadic cases have been documented in other countries among immigrants from high-risk regions.[13] It can be considered a variant of low-grade MALT lymphoma and is characterized by a diffuse lymphoplasmatic/plasmatocytic infiltrate in the proximal small bowel.[6] Persistent intestinal infection may generate chronic antigenic stimulation. This, in turn, results in the selection of a clonal IgA-secreting B-cell population that produces a mutated α-heavy chain with no light chain, which can be detected in the serum, urine, saliva, and duodenal fluid in the majority of the cases.[5,13,30] Molecular and immuno-histochemical studies have demonstrated an association of this type of lymphoma with Campylobacter jejuni. Most untreated IPSID patients progress to lymphoblastic and immunoblastic (high-grade large cell) lymphoma which invades the intestinal wall and mesenteric lymph nodes and gives rise to distant metastases.[30]

Follicular lymphoma

Gastrointestinal follicular lymphoma is very rare and is more frequently found in the small bowel and more specifically in the duodenum, than at other sites of the gastrointestinal tract. More often it is secondary to nodal disease. Patients may present with obstructive symptoms due to a mass or thickening of the bowel wall. Grossly, follicular lymphoma may appear as small polyps or ulcerative lesions, occasionally appearing as multiple lympomatous polyposis.[13] Negativity for CD5 and cyclin-D1 differentiates it from mantle cell lymphoma, which appears most commonly as multiple lymphomatous polyposis. Follicular lymphoma expresses surface Ig (frequently IgM) and pan B-cell antigens, with CD10 and bcl-2 expressed in almost 90% of cases. IgH/bcl2 rearrangement with t(14;18) (q32,q21) can be demonstrated by FISH or PCR analysis in the majority of cases.[9]

Enteropathy associated T-cell lymphoma

T-cell lymphomas are in their majority associated with coeliac disease (gluten sensitive enteropathy). Enteropathy associated T-cell lymphoma (EATL) develops after a longstanding history of coeliac disease and/or dermatitis herpetiformis. Most of the patients are in the sixth or seventh decade of life and of Irish or North American descent.[14] A threshold model for the development of celiac disease has been proposed, in which the efficiency of gluten presentation to $CD4^+$ T cells determines the likelihood of developing celiac disease and its complications such as lymphoma.[31] Deterioration in the chronic clinical picture of coelial disease with intestinal perforation is the common form of presentation. Death usually results from multifocal intestinal perforation.[14]

CLINICAL PRESENTATION AND BLOOD EXAMINATIONS

The clinical presentation of small intestine lymphoma is non-specific. Presenting symptoms are colicky abdominal pain, nausea, vomiting and, rarely, acute obstructive symptoms, intussusceptions, perforation and haemorrhage. Intermittent episodes of colicky abdominal pain and vomiting were symptoms in our patient.[4] When lymphoma is suspected as the cause of these symptoms, additional information should be gathered from the history regarding the patient's general performance status and the presence of B-symptoms (unexplained 10% loss of body weight in the preceding 6 months, persistent or recurrent fever with temperatures >38°C during the previous month, or recurrent night sweats during the previous month). Those factors can be used in the calculation of a prognostic index along with laboratory and staging data.[14] Chronic diarrhoea may be observed in some subtypes (see above).

Physical examination focuses on the presence of peripheral lymph nodes, liver and spleen enlargement, while a meticulous ENT examination is warranted. Blood examinations should include a complete blood count, liver function tests, serum LDH, uraemia, electrophoresis and immunofixation of blood proteins, β2 microglobuline levels, and EBV and HIV serology.[14]

IMAGING AND DIAGNOSIS

Radiological modalities that can suggest the diagnosis of small bowel lymphoma preoperatively include small bowel contrast studies, CT and MRI (Figures 1-3). The latter studies are gradually replacing conventional barium radiography.[32] Tumours may be large, while multiple lesions are observed in 10–25% of cases. The bowel lumen may be narrowed or enlarged, whereas there may be segments of bowel that show both features. Homogeneous wall thickening, greater than 2 cm, with a normal or an enlarged lumen, is highly suggestive of small bowel lymphoma.[32-35] The radiographic features on barium studies have been well described[35] and comprise several patterns: nodular, infiltrating, polypoid, endoexoteric (excavation and fistulation), and mesenteric invasive form (extraluminal masses). In conjunction with the infiltrative and other forms, a specific feature known as 'aneurysmal dilatation' of the bowel may occur.[33] There is localized dilatation of the lumen, with accompanying mural thickening in this segment. The dilatation is probably the result of diffuse infiltration and destruction of the muscularis propria and autonomic plexus. This appearance may be mimicked by gastrointestinal stromal tumours (GIST) and metastases from melanoma. The mesenteric invasive form is characterized by intestinal wall thickening and prominent mesenteric nodal masses. Within the mesentery, this can produce the characteristic 'hamburger sign' or 'sandwich sign'– i.e. nodal masses which surround the mesenteric vessels between mesenteric layers – on CT, MRI or ultrasound.[32,33] In our case, small bowel contrast studies showed a picture described earlier as "infiltrative form" with mural thickening and separation of folds, suggestive of small bowel lymphoma. CT and MRI findings confirmed the probable diagnosis showing mural thickening extending to the mesentery, but without the characteristic 'hamburger sign'. The radiological findings usually do not correlate with specific pathological subtypes. Certain features, however, should be particularly noted.[9] Mantle cell lymphoma, follicular lymphoma and MALT lymphoma rarely present with multiple polyps (multiple lymphomatous polyposis). Burkitt lymphoma usually presents as a bulky mass in the right lower quadrant, while IPSID tends to affect proximally with a disseminated nodular pattern leading to mucosal fold thickening, irregularity and speculation. EATL, usually proximal or diffuse, shows nodules, ulcers or strictures. EATL and peripheral T-cell lymphoma, preferentially involving the jejunum, have an increased tendency to perforate.

The definite diagnosis of small bowel lymphoma is established by histological examination. With a large proportion of small bowel lymphomas located in the vicinity of the ileocecal valve,[15] tissue for diagnosis may be obtained by means of lower gastrointestinal tract endoscopy and subsequent biopsy. Similarly, small bowel lymphoma of the duodenum and very proximal jejunum may be diagnosed with conventional enteroscopy of the upper gastrointestinal tract and biopsy. For the lesions inaccessible with conventional endoscopy, new methods of endoscopy have recently been developed. Evaluation of small bowel tumours has been revolutionized since the introduction of capsule endoscopy and double-balloon technique of push-and-pull enteroscopy.[36-42] The latter method makes it possible to obtain biopsies of any site in the small bowel. Small bowel lymphomas appear as masses, polyps, or ulcers, which cannot be macroscopically distinguished from any other lesion. Conventional and double-balloon endoscopy, whenever available, may play an important role not only in the preoperative histological diagnosis, but also in the treatment of complications of small bowel lymphomas.

In the rest of the cases, the definite diagnosis is established after surgical intervention.[14] In the case of limited localized disease, small bowel resection is an appropriate option, while open or laparoscopic biopsy seems to be indicated for diagnostic purposes in extensive disease. Besides morphology and immunohistochemistry, cytogentic and molecular biology studies may be performed on the specimen. Evaluation of expression of tumour markers and translocations may be helpful to differentiate between histological subtypes of intestinal lymphomas.[9] Frozen tissue, which allows molecular biology, is often warranted for protocol studies.[14]

In our case, the lesion was inaccessible with conventional endoscopy, while double-lumen endoscopy was unavailable for preoperative histological diagnosis of small bowel lymphoma and determination of its histological subtype. Therefore, the diagnosis of small bowel lymphoma could only be established after laparotomy and small bowel resection. Moreover, the patient's symptomatology (i.e. bowel obstruction) justified such a procedure. During follow-up gastroscopy biopsy was positive for gastric MALT lymphoma, despite the initial negative pathology findings in the preoperative gastroscopy. Unfortunately, a repeat examination of the initial specimen was not possible.

STAGING SYSTEMS

After the diagnosis, an assessment of the extent of the disease should follow. The presence of B-symptoms should be noted and CT of chest and abdomen, as well as bone marrow biopsy are needed. In order to examine further involvement of the gastrointestinal tract, upper and lower gastrointestinal tract endoscopy and small bowel enema might be indicated. During endoscopy, biopsies should be taken systematically, even when there is no macroscopic lesion. It is preferable to send those biopsies to a specialized pathologist who will search meticulously for evidence of lymphoma. Cerebrospinal fluid study might be indicated for disseminated high-grade lymphomas, for those with a significant tumour mass, or for high-grade and Burkitt lymphomas.[14] Incorporation of 18F-FDG Positron Imaging Tomography (FDG-PET) is beneficial in staging of diffuse large B cell lymphoma, follicular lymphoma and mantle cell lymphoma, but not for MALT lymphomas.[9]

Staging of small bowel and other gastrointestinal lymphomas is a matter of debate due to the variety available staging systems. Although the Musshof modification of the Ann Arbor staging system (Table 3) is feasible and relevant for prognosis,[43,44] certain demerits in terms of disseminated and incurable infiltration of the gastrointestinal tract prompted development of a new staging system by the European Gastro-Intestinal Lymphoma Study Group (EGILS).[45] As a result of discussion on staging protocols and reporting systems in the

Table 3. Clinical Ann Arbor staging system modified by Musshoff for digestive tract lymphomas[43,44].

Stage	Definition
IE	Involvement of one site of the digestive tract with no lymph node involvement
IIE	Involvement of one site of the digestive tract and regional lymph nodes with no extra-abdominal involvement
II1E	Involvement of only contiguous lymph nodes
II2E	Involvement of regional noncontiguous lymph nodes
IIIE	Localized involvement of digestive tract associated with lymph node involvement of both sides of the diaphragm
IVE	Involvement of one or several extranodal and/or extra-abdominal organs with or without associated lymph node involvement

The presence or absence of systemic symptoms should be noted with each stage designation.
A: asymptomatic; B: presence of fever, sweats, or weight loss >10 percent of body weight.

Table 4. Paris staging system for primary gastrointestinal lymphomas[45].

Tx	Lymphoma extent not specified
T0	No evidence of lymphoma
T1	Lymphoma confined to mucosa/submucosa
T1m	Lymphoma confined to mucosa
Tsm	Lymphoma confined to submucosa
T2	Lymphoma infiltrates muscularis propria or subserosa
T3	Lymphoma penetrates serosa (visceral peritoneum) without invasion of adjacent structures
T4	Lymphoma invades adjacent structures or organs
Nx	Involvement of lymph nodes not assessed
N0	No evidence of lymph node involvement
N1	Involvement of regional lymph nodes
N2	Involvement of intra-abdominal lymph nodes beyond the regional area
N3	Spread to extra-abdominal lymph nodes
Mx	Dissemination of lymphoma not assessed
M0	No evidence of extranodal dissemination
M1	Non-continuous involvement of separate site in gastro-intestinal tract
M2	Non-continuous involvement of other tissues or organs
Bx	Involvement of bone marrow not assessed
B0	No evidence of bone marrow involvement
B1	Lymphomatous involvement of bone marrow

TNM: clinical staging; pTNMB: pathological staging, for assessment of pathological N status examination of 6 or more lymph nodes required

previous years, a modified TNM staging system was proposed (Table 4), named after the first venue of the EGILS in Paris. The Paris staging system adequately records depth of tumour infiltration subdivides lymph node involvement and differentiates distant lymphoma manifestations depending on the involved organ. The use of this system in future studies will permit accurate comparison of the reported cohorts and should allow rapid accumulation of good data for proper stratification of patients for risk assessment and treatment options.

THERAPY ACCORDING TO THE HISTOLOGICAL TYPE

Despite the attempt to improve disease staging and consequently to improve its therapeutic management in the future, as discussed above, treatment of small bowel lymphoma greatly depends on its specific histological type. Depending on the different histological types of lymphoma, the role of surgery in the treatment ranges from significant to limited, underlying the preference for non-surgical establishment of the specific diagnosis. New techniques such as double-balloon enteroscopy for obtaining biopsies, may make surgical intervention unnecessary in histological lymphoma subtypes for which chemotherapy is the primary treatment of choice. However, double-balloon endoscopy is not yet widely available. Resection of the small bowel segment containing the tumour has frequently preceded treatment planning when required for diagnostic purposes or complications such as obstruction, intussusception,

haemorrhage and perforation.[13,14] Rarely, bowel resection may be unfeasible due to involvement of adjacent structures. In such cases only biopsy of the disease for histological diagnosis and surgery for relief of symptoms (i.e. by-pass of involved segments) might be indicated, followed by systemic chemotherapy. Further, in the case of multifocal involvement or advanced disease, i.e. one which has spread to extra-regional lymph nodes or extranodal dissemination, systemic chemotherapy is usually considered the primary treatment.[13,14] In general, radiotherapy is not beneficial for small bowel lymphoma due to the inconsistent intra-abdominal location of the involved small bowel segments, significant radiotherapy related local side effects, as well as the frequently observed multifocal involvement and spread of small bowel lymphoma.[9]

MALT lymphoma and diffuse large B-cell lymphoma

Surgery plays a particularly important role in the treatment of intestinal lymphomas of the marginal zone of MALT (low grade B-cell lymphomas) and diffuse large B-cell lymphomas. However, treatment with surgery alone is insufficient, even for localized disease (stages IE and IIE). After attempted curative resection, five year survival rates are only approximately 45% for stage IE and 19% for stage IIE.[46] In the early stages, combination chemotherapy may improve disease free and overall survival when compared to surgery alone, even when stages IE and IIE are considered separately.[47] In patients with advanced disease (stage IIIE and IVE) combination chemotherapy is the treatment of choice, resulting in 5-year and 10-year survival rates of 50% and 20% respectively. In this group of patients, surgery may be indicated to establish the diagnosis, while palliative surgical resection could possibly have a role prior to chemotherapy so as to prevent subsequent bleeding or perforation.[48] Palliative radiotherapy has rarely been used for extensive unresectable disease.

The systematic treatment used is one of the following: polychemotherapy with CHOP (doxorubicin, cyclophosphamide, vincristine, prednisone), COP (cyclophosphamide, vincristine, prednisone), or oral monochemotherapy using an alkylating agent (chlorambucil or cyclophosphamide) in combination with, or without, rifuximab (anti-CD20). The target of monoclonal antibody therapy with rifuximab is the CD20 antigen. In nodal NHL, the addition of rituximab to conventional CHOP chemotherapy resulted in better response and survival rates.[49]

Given the fact that chemotherapy plays a pivotal role in the treatment of intestinal lymphomas in association with the increasing incidence of preoperatively diagnosed patients, a surgeon may question whether to resect or not an asymptomatic intestinal low grade MALT or diffuse large B cell lymphoma prior to chemotherapy. Although there are no prospective randomized trials, in many series patients who had undergone surgery had better overall survival and a suggested benefit in the event free survival than those who did not.[50-52]

Mantle cell lymphoma

Mantle cell lymphomas (lymphomatous polyposis) are often disseminated with multifocal digestive tract involvement as well as bone marrow, peripheral node and blood involvement. Mantle cell lymphoma treatment response and prognosis are poor, with a short unmaintained remission after chemotherapy. In physically fit and younger (<65 years) patients, intensive chemotherapy with agents like cytarabine in high doses and with intensification, is advocated, followed by autologous haemopoietic stem-cell transplantation at the first remission. Rituximab is also used with this intensive chemotherapy.[53] In elderly subjects, CHOP combined with rituximab is frequently administered. Recently, novel agents have been developed and applied with promising results in mantle cell lymphoma patients with relapse or refractory disease.[54] Because of early dissemination and its multifocal nature, surgery in this case is only indicated for establishment of diagnosis and treatment of complications.

Follicular lymphoma

Primary follicular lymphomas of the gastrointestinal tract are very rare (<7% of all NHL in this location) and have an indolent course, even in the absence of specific treatment. Moreover, their endoscopic appearance may be identical to mantle cell lymphoma (lymphomatous polyposis). Therefore, immunophenotyping and molecular biology studies are needed for diagnosis. So as to avoid unnecessary surgical intervention, it is important to attempt to establish the diagnosis by endoscopy and biopsy, since a watch-and-wait policy is advocated by many authors for indolent early stage follicular small bowel lymphoma, until the lymphoma is symptomatic or shows evidence of progression.[9,55] The latter is based on the fact that the relapse rate in treated patients is comparable to the progression rate of untreated patients.[56] Another argument for such a watch-and-wait policy is the multifocal involvement from the distal duodenum to the terminal ileum. Surgery is only indicated for diagnosis when endoscopic harvest of biopsies has failed, and for treatment of local complications, while combination chemotherapy with CVP (cyclophosphamide, vincristine, prednisone) or CHOP in combination with rituximab is only administered for symptomatic lymphoma, or when a bulky tumour mass is present.[57-59]

Burkitt lymphoma

For Burkitt lymphoma no optimized therapeutic protocol is available. Usually, an aggressive approach is required and thus Burkitt lymphoma is treated with chemotherapy consisting of high dose cyclophosphamide, vincristine, doxorubicin, methotrexate and cytarabine for a short duration.[9,14] High dose chemotherapy and hematopoietic stem cell transplantation are beneficial for almost 50% of Burkitt cell lymphoma patients.[60] If the diagnosis is established and there are no complications that require immediate surgery, there is no indication for surgery in the treatment regimen.

Immunoproliferative small intestine disease – alpha chain disease

For this lymphoma type, surgery is also not advocated as a primary treatment option. Early stage disease is initially treated only with antibiotic therapy, with tetracyclines, or combined metronidazole and ampicillin, with a remission occurring in 6-12 months.[13] Intermediate or advanced stage disease benefit from anthracycline-based chemotherapy, in addition to tetracycline.[13] In the case of treatment failure and in patients with disseminated disease, intensive chemotherapy with autologous bone marrow transplantation has been recommended,[14] but in these situations prognosis remains poor and recurrence usually occurs rapidly. Surgery plays a limited therapeutic role in the majority of cases due to diffuse involvement.[9]

Enteropathy associated T-cell lymphoma

For overt enteropathy associated T-cell lymphoma (EATL), a mainstay treatment is anthracyclin-based chemotherapy. Because of the poor response to treatment with only chemotherapy and because of related complications, such as perforation, approaches including surgery to remove gross disease prior to chemotherapy are recommended.[9] It has been reported that 66% of EATL patients undergoing surgical resection followed by combined chemotherapy and autologous stem cell transplantation can achieve a sustained complete response.[61]

FOLLOW-UP AND PROGNOSIS

Repetition of the initial work up after treatment completion and a subsequent annual ten year follow-up, which includes physical examination, biochemical tests (LDH level, beta-2 microglobulinemia, liver function tests), CT of chest and abdomen, and endoscopic examination of the initially involved sites is recommended. Bone marrow biopsy is necessary only if there had been initial involvement.[14] There is evidence that FDG-PET has better sensitivity and specificity, as well

as better positive and negative predictive values than CT in the post-treatment follow-up. FDG-PET can have potential value in monitoring the treatment response.[62]

The estimated 5-year overall survival and event-free survival of small bowel lymphoma are approximately 80% and 65%, respectively,[15] but vary according to the histological type, stage and treatment modality. For intestinal low grade B-cell lymphoma, the percentages have been reported to be approximately 85-90% and 55-75%, respectively,[15,63] and for intestinal high grade B-cell lymphoma approximately 60-80% and 60-70%, respectively.[15,64] Intestinal T-cell lymphoma do generally worse; an estimated 5-year survival rate of less than 40% and an event-free survival rate of approximately 25% have been reported in a recent series.[15] The international prognostic index, initially developed for diffuse large B-cell lymphoma, is, at present, the most valuable and widely used for prognostic stratification of almost all subtypes of non Hodgkin lymphoma. The risk of death is determined from low to high by the number of adverse risk factors observed, including age >60 years, ≥2 extranodal sites, Ann Arbor stage III-IV, performance status ≥2 (ECOG) and high lactate dehydrogenase.[9]

During follow-up for intestinal lymphoma, relapses are most frequently observed in lymph nodes, lung and stomach, and less often in other intestinal locations, gallbladder and breast.[22] This analysis also supports the aforementioned follow-up plan which can be summarized as limited to the primary, dominantly involved MALT organ system (including the regional lymph nodes) as well as the lungs and stomach as sites at risk of relapse. As in all types of non-gastric MALT lymphoma, a high percentage of relapse is observed in the gastric mucosa (18% of all relapse sites), as in the present case. This gastric relapses are often associated with *Helicobacter* Pylori, special emphasis should be given to the diagnosis and treatment of *Helicobacer Pylori* infection at presentation and during follow-up.[22]

THE SURGEON'S ROLE IN CONCLUSION AND FUTURE PERSPECTIVE

So what should the surgeon do when asked to consult for a patient with imaging studies suggestive of small bowel lymphoma? Notably, surgical intervention is rather often not the initial option for diagnosis or treatment. Although imaging studies may be indicative of the diagnosis, the definite diagnosis requires histological examination. When the lesion is located in a very proximal or distal part of the small bowel, endoscopic biopsy may provide histological evidence. Most recently, advanced modalities such as double balloon endoscopy have been reported to be effective in obtaining biopsies from lesions in more remote areas. Unfortunately, this method is not widely available yet and experience is still limited. When endoscopic biopsy is not possible, surgery is indicated for histological confirmation. Intestinal resection is usually performed when a small segment is involved, while open or laparoscopic biopsy is an option for advanced disease. With increasing application of double balloon endoscopy, surgery for diagnostic purposes will be significantly limited in the near future.

In many subtypes of uncomplicated histologically proven small bowel lymphoma surgery may not be indicated at all. The surgeon's role in the treatment of small bowel lymphomas depends on the histological type, the extent of the disease and the occurrence of complications. Unfortunately, because of their rarity and variety, there are few prospective trials concerning their therapeutic management, rendering it difficult to draw specific guidelines. However, there is evidence in the case of locoregional disease that surgical resection of the primary tumour with its regional lymph nodes in combination with chemotherapy improves outcomes in some types of small bowel lymphomas, including lymphomas of the marginal zone of MALT, diffuse large B cell lymphomas and EATL. For other histological types, surgery

is not indicated as primary treatment, mainly due to initial or early disease course presence of advanced disease, multifocal involvement or recurrence. Nevertheless, surgery may be needed for treatment of complications such as bleeding, stenosis and perforation even before the diagnosis is established, as in the presented case. Such surgical intervention may be necessary in an emergent setting. When a suspect small bowel lesion is encountered intra-operatively and in the absence of a preoperative histological diagnosis, adequate wide resection of the involved bowel segment and its adjacent mesentery is advocated, when possible. Otherwise, symptom relief and harvest of tissue adequate for diagnosis should be assured.

There has been tremendous progress in the diagnosis, staging and management of intestinal lymphoma in the last two decades. Due to improved insight into its pathogenesis and molecular biology, novel monoclonal antibodies and addition of cytokines and other immune modulators have been used with promising preliminary results.[65,66] Another important aspect is the increased diagnostic efficacy of imaging techniques and the wider availability of double balloon endoscopy in the diagnosis of lymphomas. Molecular imaging and radioimmunotherapy with a variety of new radiopharmaceutical agents that target the upregulated specific receptors in lymphoma cells are emerging field.[67,68] All these new developments will further decrease the need for surgical intervention for diagnosis and treatment of intestinal lymphoma in the future.

ACKNOWLEDGEMENT

We would like to thank Mrs. Eugenia Bolbasis for the linguistic review of this manuscript.

REFERENCES

1. Zollinger RM Jr. Primary neoplasms of the small intestine. *Am Surg* 1986; 151: 654-658.
2. Ashley SW, Wells SA Jr. Tumors of the small intestine. *Semin Oncol* 1988; 15: 116-128.
3. Frost DB, Mercado PD. Tyrell JS. Small bowel cancer: a 30-year review. *Ann Surg Oncol* 1994;1:290-295.
4. Schottenfeld D, Beebe-Dimmer JL, Vigneau FD. The epidemiology and pathogenesis of neoplasia in the small intestine. *Ann Epidemiol* 2009; 19: 58-69.
5. Du M-Q. MALT lymphoma: recent advances in aetiology and molecular genetics. *J Clin Exp Hematopathol* 2007; 47: 31-42.
6. Zucca E, Roggero E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 1: Gastrointestinal, cutaneous and genitourinary lymphomas. *Ann Oncol* 1997; 8: 727-737.
7. Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. *Br J Surg* 1961; 49: 80-89.
8. Devesa SS, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. *Cancer Res* 1992; 52: S5432-S5440.
9. Ghimire P, WU G-Y, Zhu L. Primary gastrointestinal lymphoma. *World J Gastroenterol* 2011; 17: 697-707.
10. Weisenburger DD. Epidemiology of non-Hodgkin's lymphoma: Recent findings regarding an emerging epidemic. *Ann Oncol* 1994; 5: S19-S24.
11. MacDonald TT. The mucosal immune system. *Parasite Immunol* 2003;25:235–246.
12. Suarez F, Lortholary O, Hermine O, Lecuit M. Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven lymphoproliferation. *Blood* 2006; 107: 3034-3044.
13. Dickson BC, Serra S, Chetty R. Primary gastrointestinal tract lymphoma; diagnosis and management of common neoplasms. *Expert Rev Anticancer Ther* 2006; 6: 1609-1628.
14. Ruskone Fourmestraux A. Gastro-intestinal lymphomas. *Gastroenterol Clin Biol* 2006; 30: S81-S90.
15. Wang G-B, Xu G-L, Luo G-Y, et al. Primary intestinal non-Hodgkin's lymphoma; A clinicopathologic analysis of 81 patients. *World J Gastroenterol* 2011; 17: 4625-4631.
16. Thieblemont C, Berger F, Dumontet C, et al. Mucosa-associated lymphoid tissue lymphoma is a disseminate disease in one third of 158 patients analyzed. *Blood* 2000; 95: 802-806.
17. Isaacson PG, Du MQ. MALT lymphoma from morphology to molecules. *Nat Rev Cancer* 2004; 4: 644-653.
18. Montalban C, Castrillo J, Abraira V, et al. Gastric B-cell mucosa-associated lymphoid tissue (MALT)

lymphoma: clinicopathological study and evaluation of the prognostic factors in 143 patients. *Ann Oncol* 1995; 6: 355-362.
19. Zizani P, Magagnoli M, Galieni P, et al. Non gastrointestinal low-grade mucosa-associated lymphoid tissue lymphoma: analysis of 75 patients. *J Clin Oncol* 1999; 17: 1254-1258.
20. Arcaini L, Burcheri S, Rossi A, et al. Nongastric marginal-Zone B-Cell MALT Lymphoma: prognostic value of disease dissemination. *Oncologist* 2006; 11: 285-291.
21. Sretonovic M, Colovic M, Jankovic G, et al. More than a third of non-gastric malt lymphomas are disseminated at diagnosis: a single center survey. *Eur J Haematol* 2009; 82: 373-380.
22. de Boer JP, Hiddnick RF, Raderer M, et al. Dissemination patterns in non-gastric MALT lymphoma. *Haematologica* 2008; 93: 201-206.
23. Stephen MR, Farquharson MA, Sharp RA, Jackson R. Sequential malt lymphomas of the stomach, small intestine and gall bladder. *J Clin Pathol* 1998; 51: 75-82.
24. Venizelos J, Tamiolakis D, Nikolaidou S, Lambropoulou M, Alexiadis G, Papadopoulos N. Concurrent low grade B-cell non Hodgkin's lymphoma of MALT type arising in the large intestine, small intestine and stomach. *Chirurgia* 2007; 102: 99-101.
25. Isaacson P. The MALT lymphoma concept updated. *Ann Oncol* 1995; 6: 319-320.
26. Dogan A, Du M, Koulis A, Briskin M, Isaacson P. Expression of lymphocyte homing receptors and vascular addressing in low-grade gastric B-cell lymphomas of mucosae-associated lymphoid tissue. *Am J Pathol* 1997; 151: 1361-1369.
27. Du MQ, Xu CF, Diss TC et al. Intestinal dissemination of gastric mucosa-associated lymphoid tissue lymphoma. *Blood* 1996; 88: 4445-4451.
28. Nguyen V, Nguyen B, Petris GD, Nguyen C. Education and imaging. Gastrointestinal: gastrointestinal involvement of mantle cell lymphoma *J Gastroenterol Hepatol* 2012; 27: 617.
29. Arora N, Manipadam MT, Pulimood A, et al. Gastrointestinal lymphomas: pattern of distribution and histological subtypes: 10 years experience in a tertiary centre in South India. *Indian J Pathol Microbiol* 2011; 54: 712-719.
30. Al-Saleem T, Al-Mondhiry H. Immunoproliferative small intestinal disease (IPSID): a model for mature B-cell neoplasms. *Blood* 2005; 105: 2274-2280.
31. Tjon JM, van Bergen J, Koning F. Celiac disease: how complicated can it get? *Immunogenetics* 2010; 62: 641-651.
32. Anzidei M, Napoli A, Zini C, Kirchin MA, Catalano C, Passariello R. Malignant tumours of the small intestine: a review of histopathology, multidetector CT and MRI aspects. *Br J Radiol* 2011; 84: 677-690.
33. Mendelson RM, Fermoyle S. Primary gastrointestinal lymphomas: A radiological–pathological review. Part 2: Small intestine. *Aust Radiol* 2006; 50: 102–113.
34. Ghai S, Pattison J, Ghai S, O'Malley ME, Khalili K, Stephens M. Gastrointestinal lymphoma: spectrum of imaging findings with pathologic correlation. *Radiographics* 2007; 27: 1371-1388.
35. Gourtsogiannis NC, Nolan J. Lymphoma of the small intestine: radiological appearances. *Clin Radiol* 1988; 39: 639-645.
36. Tamura H, Ogata K, Kondo A, et al. Double balloon endoscopy as a useful tool for the diagnosis and treatment of four cases of primary small intestinal lymphoma. *Rinsho Ketsuki* 2007; 48: 510-513.
37. Almeida N, Figueiredo P, Lopes S, Gouveia H, Leitão MC. Double balloon endoscopy and small bowel tumors: a South- European single – center experience. *Dig Dis Sci* 2009; 54: 1520-1524.
38. Imaoka H, Higaki N, Kumagi T, et al. Characteristics of small bowel tumors detected by double balloon endoscopy. *Dig Dis Sci* 2011; 56: 2266-2371.
39. Lee BI, Choi H, Choi KY, et al. Clinical characteristics of small bowel tumors diagnosed by double-balloon endoscopy. KASID multi-center study. *Dig Dis Sci* 2011; 56: 2920-2927.
40. Rondonotti E, Pennazio M, Toth E, et al; European Capsule Endoscopy Group; Italian Club for Capsule Endoscopy (CICE); Iberian Group for Capsule Endoscopy. Small-bowel neoplasms in patients undergoing video capsule endoscopy: a multicenter European study. *Endoscopy* 2008; 40: 488-495.
41. Trifan A, Singeap AM, Cojocariu C, Sfarti C, Tarcoveanu E, Georgescu S. Small bowel tumors in patients undergoing capsule endoscopy: a singlecenter experience. *J Gastrointest Liver Dis* 2010; 19: 21-25.
42. Sidhu R, McAlindon ME. The use of capsule endoscopy for the investigation of small bowel tumors: experience from a United Kingdom single center. *Dig Dis Sci* 2011; 56: 2763.
43. Rosenberg SA. Validity of the Ann Arbor staging classification for the non-Hodgkin's lymphomas. *Cancer Treat Rep* 1977; 61: 1023.
44. Moormeier JA, Williams SF, Golomb HM. The stag-

ing of non-Hodgkin's lymphomas. *Semin Oncol* 1990; 17: 43-50.
45. Ruskoné-Fourmestraux A, Dragosics B, Morgner A, Wotherspoon A, de Jong D. Paris staging system for primary gastrointestinal lymphomas. *Gut* 2003; 52: 912-913.
46. Domizio P, Owen R, Shepherd, Talbot IC, Norton AJ. Primary lymphoma of the small intestine: A clinicopathological study of 119 cases. *Am J Surg Pathol* 1993; 17: 429-442.
47. Daum S, Ullrich R, Heise W, et al. Intestinal non-Hodgkins lymphoma: a multicenter prospective clinical study from the German study Group on Intestinal non-Hodgkin lymphoma. *J Clin Oncology* 2003; 21: 2740- 2746.
48. Racker V, Thirlby R, Ryan J. Role of surgery in multimodality therapy for gastrointestinal lymphoma. *Am J Surg* 1991; 161: 570-575.
49. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; 346: 235-242.
50. Ibrahim EM, Ezzat AA, El-Weshi AN, et al. Primary intestinal diffuse large B-cell non-Hodgkin's lymphoma: clinical features, management, and prognosis of 66 patients. *Ann Oncol* 2001; 12: 53-58.
51. Radaszkiewicz T, Bragosics B, Bauer P. Gastrointesinal malignant lymphomas of the mucosa associated lymphoid tissue, factors relevant to prognosis. *Gastroenterology* 1992; 102: 1628-1638.
52. D'Amore F, Brincker H, Gronbaek K, et al. Non-Hodgkins lymphoma of the gastrointestinal tract. A population based analysis of incidence, geographic distribution, clinicopathological presentation features and prognosis. *J Clin* Oncol 1994; 12: 1673-1684.
53. Brugger W, Hirsch J, Grunebach F, Repp R. Rituximab consolidation after high-dose chemotherapy and autologous blood stem cell transplantation in follicular and mantle cell lymphoma: a prospective, multicenter phase II study. *Ann Oncol* 2004; 15: 1691-1697.
54. Ogura M. Current treatment strategy and new agents in mantle cell lymphoma. *Int J Hematol* 2010; 92: 25-32
55. Bennani-Baiti N, Daw HA, Cotta C, et al. Low-grade follicular lymphoma of the small intestine: a challenge for management. *Semin Oncol* 2011; 38: 714-720.
56. Yamamoto S, Nakase H, Yamashita K, et al. Gastrointestinal follicular lymphoma: review of the literature. *J Gastroenterol* 2010; 45: 370-388.
57. Tari A, Asaoku H, Kunihiro M, Tanaka S, Fuijhara M, Yoshino T. Clinical features of gastrointestinal lymphoma: comparison with nodal follicular lymphoma and gastrointestinal MALT lymphoma. *Digestion* 2011; 83: 191-197.
58. Damaj G, Verkarre V, Delmer A, et al. Primary follicular lymphoma of the gastrointestinal tract: a study of 25 cases and a literature review. *Ann Oncol* 2003; 14: 623-629.
59. Seymour JF. New treatment approaches to indolent non-Hodgkin's lymphoma. *Semin Oncol* 2004; 31: 27-32.
60. Song KW, Barnett MJ, Gascoyne RD, et al. Haematopoietic stem cell transplantation as primary therapy of sporadic adult Burkitt lymphoma. *Br J Haematol* 2006; 133: 634-637.
61. Bishton MJ, Haynes AP. Combination chemotherapy followed by autologous stem cell transplant for enteropathy-associated T cell lymphoma. *Br J Haematol* 2007; 136: 111-113.
62. Kumar R, Xiu Y, Potenta S, Mavi A, et al. 18F-FDG PET for the Evaluation of the treatment response in patients with gastrointestinal tract lymphomas. *J Nucl Med* 2004; 45: 1796-1803.
63. Oh SY, Suh C. Non-gastric marginal zone B-cell lymphoma in Korea: clinical features, treatment, and prognostic factors. *Korean J Intern Med* 2010; 25: 227-236.
64. Ibrahim EM, Ezzat AA, El-Weshi AN, et al. Primary intestinal diffuse large B-cell non-Hodgkin's lymphoma: Clinical features, management, and prognosis of 66 patients. *Ann Oncol* 2001; 12: 53-58.
65. Paoluzzi L, Kitagawa Y, Kalac M, Zain J, O'Conner OA. New drugs for the treatment of lymphoma. *Hematol Oncol Clin North Am* 2008; 22: 1007-1035.
66. Elstrom RI, Martin P, Leonard JP. New biological agents and immunological strategies. *Hematol Oncol Clin North Am* 2008; 22: 1037-1049.
67. Iagaru A, Goris ML, Gambhir SS. Perspectives of molecular imaging and radioimmunotherapy in lymphoma. *Radiol Clin North Am* 2008; 46: 243-252.
68. Natarajan A, Gowrishankar G, Nielsen CH, et al. Positron emission tomography of (64)Cu-DOTA-Rituximab in a transgenic mouse model expressing human CD20 for clinical translation to image NHL. *Mol Imaging Biol* 2012; 14: 608-616.

HELLENIC SURGICAL ONCOLOGY 2014; 5(2): 74-79

REVIEW

Electrochemotherapy in the head and neck area
An addition to the surgical armentarium

R. de Bree, D.A. Heuveling

Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands

ABSTRACT

Electrochemotherapy (ECT) is a treatment modality that combines administration of a chemotherapeutic drug, e.g. bleomycin, with electroporation therapy (EPT). EPT uses brief, high-intensity, pulsed electrical currents to enhance the uptake of cytotoxic drugs by producing a transient increase in cell wall permeability. ECT increases the effect of cytostatic drugs, is independent of histology of the lesion, enables treatment to previously treated areas, preserves healthy tissue, has no significant side effects (low dose chemotherapy) and enables repeated treatments. ECT is an addition to the current treatment options of head and neck cancer.

KEY WORDS: head and neck cancer; skin cancer; electroporation; bleomycin; electrochemotherapy

INTRODUCTION

Early stage head and neck cancer has a favourable prognosis and is usually treated with surgery or radiotherapy. Approximately two-thirds of the patients present with advanced stage disease and are generally treated with a combination of surgery and radiotherapy or concomitant radiotherapy and chemotherapy. Nevertheless, 10% to 30% of these patients will develop a local recurrence, 10 to 20% a regional recurrence, while second primary tumours frequently develop in these patients at a rate of 2% to 3% per annum. Treatment of these second primary tumours is challenging, especially when the site has already been subjected to extensive surgery, or when radiotherapy is no longer an option because of previous treatment.[1] Furthermore, primary cutaneous malignancies, and infrequently occurring cutaneous metastases, may be particularly troublesome to the patient. Surgical resection may lead to functional and esthetical problems, and if radiotherapy is no longer an option, chemotherapy as monotherapy can usually only be used palliatively.

Important negative outcomes after treatment of head and neck cancer are problems caused by loss of function (swallowing and speech) and

Correspondence address:
Remco de Bree, MD, PhD, Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center, De Boelelaan 1117,
PO Box 7057, 1007 MB Amsterdam, The Netherlands,
Tel.: +31-20-4443690; Fax: +31-20-4443688; e-mail r.bree@vumc.nl

cosmetic disfigurement. The restrictions caused by earlier treatments and the need for function-sparing therapy have motivated the development of new techniques to treat head and neck cancer. An example of one such technique is electrochemotherapy (ECT).

ELECTROCHEMOTHERAPY

The technology to deliver ECT has been developed within the 5th FP: Cliniporator project (Cliniporator, QLK3-1999-00484). The European Commission funded a second project ESOPE (European Standard Operating Procedures for Electrochemotherapy and Electrogenetherapy) to sponsor a multicenter clinical study that demonstrated the efficacy of ECT for the treatment of metastatic nodules located at the skin or in subcutaneous tissue.

Electrodes, configured as arrays of 6 to 8 needles, or 2 parallel plates, are used to deliver electrical pulses to the tumour, so called electroporation (EPT); the electrode separation and relative position is fixed, thus the electrical pulse amplitude is defined in the device based on the individual electrode geometry. Presently, effective electric pulse protocols have been identified and used both for drug and gene electrotransfer to cells. For the purpose of ECT a standardized electric pulse protocol has been identified and is delivered to the tumour nodule 8 minutes after intravenous injection of (relatively low dose) bleomycin, or intratumourally for bleomycin and cisplatin dosed accordingly to tumour volume.[2,3]

In vitro ECT studies have shown bleomycin to be the most effective cytostaticum for the destruction of tumour cells.[4,5] After entering the cell, bleomycin can become effective.[6] The cytotoxicity of bleomycin is enhanced 300- to 700-fold by the electroporation procedure.[7] Due to the electroporation of cells membranes, the extracellular concentrations of bleomycin can be very low while still being effective on tumour cells.[8] It is important to realize that the procedure leads to poration only in the area encased by the needle-electrodes, therefore it is necessary to treat the tumour in overlapping fields to bring about poration of the whole tumour.[9] EPT without bleomycin had no effect on tumour tissue. In tumour-bearing animals, no seeding of tumour cells via needle-electrodes was detected while the treatment around arteries did not provoke any problems either.[10] Bloom and Goldfarb[11] showed that bleomycin with EPT had a significantly greater number of patients showing objective response to therapy when compared to bleomycin administration alone. A recent meta-analysis confirmed that ECT had significantly higher effectiveness (by more than 50%) than bleomycin and cisplatin alone.[12] Since ECT using bleomycin is a tumour cell-specific treatment (normal cells are much less sensitive to bleomycin), this therapy can be applied with ample margins, without causing substantial damage to surrounding tissue.[13]

CLINICAL STUDIES ON ELECTROCHEMOTHERAPY

ECT is a highly efficient treatment of cutaneous and subcutaneous metastatic lesions, independent of origin and independent of previous treatments, and local treatment of recurrent tumours of the skin. The clinical strength of ECT as an additional option to existing anti-tumour therapies was first demonstrated by Reintgen et al[14] and Glass et al[15] Later studies with patients with e.g., basal cell carcinoma and metastasised melanoma have shown the occurrence of a selective tumour effect with this technique, while sparing healthy tissue.[13,16-21]

Following the development of the Standard Operating Procedure (SOR) and the publication of the results of the ESOPE Project,[22] extensive clinical experience gathered in Europe has confirmed the high efficacy and success rate of the ECT. A systematic review and meta-analysis of 44 studies with 1894 tumours showed an objective response rate of 84.1% and a complete response rate of 59.4%. The objective response increased

significantly after publication of SOR.[12] The ECT technology has been disseminated and is already successfully being used in more than 60 hospitals in the EU for various cutaneous and subcutaneous tumour nodules. At the European Institute of Oncology, 108 evaluable patients with superficial malignant lesions were treated with ECT. For metastatic melanoma, the overall response rate was 88% (72% complete response) and for non-melanoma lesions the rate was 76% (67% complete response). The treatment was well tolerated either under general or local anaesthesia with minimal side effects.[23] Campana et al[24] reported an objective response to ECT in 80 out of 85 (94%) patients with superficially disseminated melanoma metastases unsuitable for resection and unresponsive to chemotherapy: 41 (48%) complete responses after one treatment and 19 (22%) after two treatments. Patients with fewer and smaller (<3 cm) had a higher local response rate.[24] Di Monta et al[25] reported successful treatment of Kaposi sarcoma with ECT (intravenous administration of bleomycin): in 14 of 19 patients displaying complete response after one treatment, and in 3 and 2 patients after 2 and 3 treatments, respectively. A recent meta-analysis on efficacy on skin directed therapy for cutaneous metastases of advanced cancer in 11 studies showed an objective response rate for ECT of 75.4% and a complete response rate of 47.5%.[26]

ECT appeared to be more cost-effective compared to radiotherapy, hyperthermia associated with radiotherapy, interferon-alpha and isolated limb perfusion for the control and treatment of cutaneous and subcutaneous neoplasms.[27] New ECT approaches are currently being developed for treatment of more deeply seated tumours.[28]

ELECTROCHEMOTHERAPY IN HEAD AND NECK CANCER

A limited number of studies reported on ECT with intratumoural injection of bleomycin in head and neck cancer patients. In the first series,[9-11] of 84 patients with head and neck cancer were treated in these trials (64 patients in stages III and IV of the disease, and 20 in stages I and II), which amounted to the treatment of a total of 99 tumours. Of the patients in advanced stages of the disease, 59% responded, while 22% showed complete remission. Patients in early stages of the disease showed a response rate of 100%, of whom 84% were in complete remission. The most important and most frequently occurring side effect (in 78% of the cases) was localized pain at the treatment site. Adverse reactions such as necrosis, oedema, and erythema were frequently observed (14-47%). Bleeding was an infrequently occurring side effect (10%). ECT was easy to perform and well tolerated.[19-21] Similar results were reported in two open-label, multicenter, single-arm Phase II studies in which 54 patients were treated with electroporation and intratumoural injected bleomycin therapy.[11] Tijink et al[29] reported on ECT using intratumoural injections of bleomycin of 17 head and neck mucosal and skin cancers which could no longer be treated with surgery or radiotherapy, or for which conventional treatment would be very invasive. All 17 tumours responded to treatment. Although the patient population consisted of patients who had already been heavily treated with conventional therapies, local tumour control was reached with ECT in 14 of the 17 (82%) tumours. In all cases, functions were preserved successfully, while the treatment minimized adverse cosmetic results. The burden on the patient was limited and not experienced as being severe. Any pain experienced was well treatable with medication. They described that, typically, within a few days after the treatment, crusting occurs at the tumour site, under which necrosis of the tumour took place. In general, the crust disappeared after 10-14 weeks, and the tumour was replaced by scar tissue (Figure 1). Tumours in the mucosa of the mouth reacted faster than those of the skin, and the wound healed completely after 8 weeks.[29] Gargiulo et al[30] reported their results of ECT using intravenous bleomycin on tumours in 25 non-melanoma cuta-

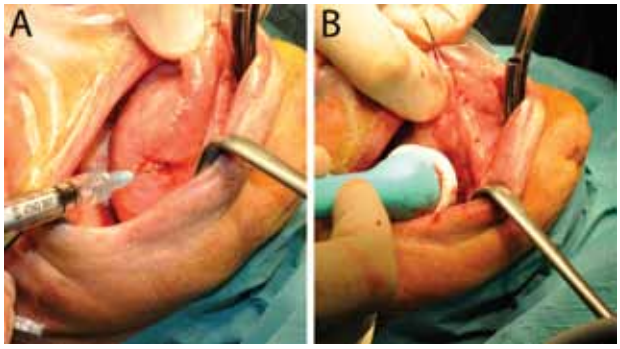

Figure 1. Local injection of bleomycin in recurrent tongue carcinoma (A) followed by electroporation using applicator with hexagonal placed needles (B).

neous and subcutaneous cancers in the head and neck region. An objective response was achieved in all patients, whereas the complete response rate was 72%. Mevio et al[31] evaluated ECT using intravenously injected bleomycin of 31 lesions (of which 2 were lymph nodes) in 14 patients with recurrent head and neck cancer not suitable for standard therapeutic options. An objective response rate of 94% was found: 61.5% complete response, 32.5% partial response, 3% stable disease and 3% progressive disease. All the lesions that underwent complete response were smaller than 3 cm. Recently, Seccia et al[32] published their results of palliative ECT in 14 locally recurrent or metastatic mucosal and skin cancers: 4/14 lesions exhibited a complete response, 6/14 partial response and in 4/14 progression of disease was observed. Campana et al[33] retrospectively reviewed the databases of two centres and found 39 patients with squamous cell carcinoma of the oral cavity or oropharynx (n=12) and non-melanoma skin cancer (n=27) and found a complete response rate of 38%, which was associated with whether the tumour was primary or recurrent and with the size and route by which the drug was given. Primary tumours, tumours less than 2 cm, intratumoural injection and tumours being chemonaive were predictive factors for better response and/or local control. The skin and mucosal tumours showed comparable complete responses and local control. Basal cell carcinoma does probably better than squamous cell carcinoma.[33]

Although experience in the head and neck area is mainly obtained from skin cancers and to a lesser extent, from mucosal cancers, other tumour types can also be treated successfully. Local control of a large local recurrence of a soft tissue sarcoma has been reported.[34]

CONCLUSION

Since in most studies heterogeneous groups of patients are treated and studies differ in inclusion of tumour types and previous treatments, the effectiveness of ECT cannot be analyzed uniformally. However, it can be concluded that ECT is an easily performed treatment, can be performed and repeated in previously treated areas, causes little burden on the patient, is potentially effective independent of histology and is an addition to the current treatment options in patients with tumours in the head and neck area.

REFERENCES

1. De Bree R, Leemans CR. New developments for optimal management of head and neck cancer. *Onkologie* 2004; 27: 339-342.
2. Mir LM, Morsli N, Garbay JR, Billard V, Robert C, Marty M. Electrochemotherapy: a new treatment of solid tumors. *J Exp Clin Cancer Res* 2003; 22: suppl 4: 145-148.
3. Mir LM, Gehl J, Sersa G, et al. Standard operating procedures of electrochemotherapy: Instructions for the use of bleomycin or ciplatin administered either systemically or locally and electric pulses delivered by the Cliniporator by means of invasive and non-invasive electrodes. *Eur J Cancer* 2006; 4: suppl 4: 14-25.
4. Mir LM, Orlowski S, Belehradek J Jr, et al. Electrochemotherapy potentiation of antitumor effect of bleomycin by local electric pulses. *Eur J Cancer* 1991; 27: 68-72.
5. Okino M, Tomie H, Kanesada H, et al. Optimal electric conditions in electrical impulse chemotherapy. *Jpn J Cancer Res* 1992; 83: 1095-1101.

6. Domenge C, Orlowski S, Luboinski B, et al. Antitumor electrochemotherapy: new advances in the clinical protocol. *Cancer* 1996; 77: 956-963.
7. Larkin JO, Collins CG, Aarons S, et al. Electrochemotherapy: aspects of preclinical development and early clinical experience. *Ann Surg* 2007; 245: 469-479.
8. Chen C, Smye SW, Robinson MP, Evans JA. Membrane electroporation theories: a review. *Med Biol Eng Comput* 2006; 44: 5-14.
9. Mossop BJ, Barr RC, Henshaw JW, Yuan F. Electric fields around and within single cells during electroporation a model study. *Ann Biomed Eng* 2007; 35: 1264-1275.
10. Gothelf A, Mir LM, Gehl J. Electrochemotherapy: results of cancer treatment using enhanced delivery of bleomycin by electroporation. *Cancer Treat Rev* 2003; 29: 371-387.
11. Bloom DC, Goldfarb PM. The role of intratumour therapy with electroporation and bleomycin in the management of advanced squamous cell carcinoma of the head and neck. *Eur J Surg Oncol* 2005; 31: 1029-1035.
12. Mali B, Jarm T, Snoj M, Sersa G, Miklavcic D. Antitumor effectiveness of electrochemotherapy: a systematic review and meta-analysis. *Eur J Surg Oncol* 2013; 39: 4-16.
13. Heller R, Jaroszeski MJ, Reintgen DS, et al. Treatment of cutaneous and subcutaneous tumors with electrochemotherapy using intralesional bleomycin. *Cancer* 1996; 83; 148-157.
14. Reintgen DS, Jaroszenski MJ, Heller R. Electrochemotherapy, a novel approach to cancer. *Skin Cancer Found J* 1996; 14: 17-19.
15. Glass LF, Pepine ML, Fenske NA, et al. Bleomycin-mediated electrochemotherapy of metastatic melanoma. *Arch Dermatol* 1996; 132: 1353-1357.
16. Byrne CM, Thompson JF, Johnston H, et al. Treatment of metastatic melanoma using electroporation therapy with bleomycin (electrochemotherapy). *Melanoma Res* 2005; 15: 45-51.
17. Glass LF, Jaroszeski M, Gilbert R, et al. Intralesional bleomycin-mediated electrochemotherapy in 20 patients with basal cell carcinoma. *J Am Acad Dermatol* 1997; 37: 596-599.
18. Mir LM, Glass LF, Sersa G, et al. Effective treatment of cutaneous and subcutaneous malignant tumours by electrochemotherapy. *Br J Cancer* 1998; 77: 2336-2342.
19. Panje WR, Hier MP, Garman GR, et al. Electroporation therapy of head and neck cancer. *Ann Otol Rhinol Laryngol* 1998; 107: 779-785.
20. Allegretti JP, Panje WR. Electroporation therapy for head and neck cancer including carotid artery involvement. *Laryngoscope* 2001; 111: 52-56.
21. Burian M, Formanek M, Regele H. Electroporation therapy in head and neck cancer. *Acta Otolaryngol* 2003; 123: 264-268.
22. Marty M, Sersa G, Garbay JR. Electrochemotherapy - An easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: Results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study. *Eur J Cancer* 2006; 4: suppl 4: 3-13.
23. Testori A, Faries MB, Thompson JF, et al. Local and intralesional therapy of in-transit melanoma metastases. *J Surg Oncol* 2011; 104: 391-396.
24. Campana LG, Valpione S, Mocellin S, et al. Electrochemotherapy for disseminated superficial metastases from malignant melanoma. *Br J Surg* 2012; 99: 821-830.
25. Di Monta G, Caracò C, Benedetto L, et al. Electrochemotherapy as "new standard of care" treatment for cutaneous Kaposi's sarcoma. *Eur J Surg Oncol* 2014; 40: 61-66.
26. Spratt DE, Gordon Spratt EA, Wu S, et al. Efficacy of skin-directed therapy for cutaneous metastases from advanced cancer: a meta-analysis. *J Clin Oncol* 2014; 32: 3144-3155.
27. Colombo GL, Matteo SD, Mir LM. Cost-effectiveness analysis of electrochemotherapy with the Cliniporatorvs other methods for the control and treatment of cutaneous and subcutaneous tumors. *Ther Clin Risk Manag* 2008; 4: 541-548.
28. Agerholm-Larsen B, Iversen HK, Ibsen P, et al. Preclinical validation of electrochemotherapy as an effective treatment for brain tumors. *Cancer Res* 2011; 71: 3753-3662.
29. Tijink BM, de Bree R, van Dongen GAMS, Leemans CR. How we do it: Chemo-electroporation in the head and neck for otherwise untreatable patients. *Clin Otolaryngol* 2006; 31: 447-451.
30. Gargiulo M, Papa A, Capasso P, Moio M, Cubicciotti E, Parascandolo S. Electrochemotherapy for non-melanoma head and neck cancers: clinical outcomes in 25 patients. *Ann Surg* 2012; 255: 1158-1164.
31. Mevio N, Bertino G, Occhini A, et al. Electrochemotherapy for the treatment of recurrent head and neck cancers: preliminary results. *Tumori* 2012; 98: 308-313.

32. Seccia V, Muscatello L, Dallan I, et al. Electrochemotherapy and its controversial results in patients with head and neck cancer. *Anticancer Res* 2014; 34: 967-972.
33. Campana LG, Mali B, Sersa G, et al. Electrochemotherapy in non-melanoma head and neck cancers: a retrospective analysis of the treated cases. *Br J Oral Maxillofac Surg* 2014 Sep 1 [Epub ahead of print].
34. de Bree R, Tijink BM, van Groeningen CJ, Leemans CR. Electroporation therapy in soft tissue sarcoma: a potentially effective novel treatment. *Sarcoma* 2006; 2006: 85234.

HELLENIC SURGICAL ONCOLOGY 2014; 5(2): 80-83

ORIGINAL PAPER

The effectiveness of TachoSil® as haemostatic agent in thyroid surgery

J. Spiliotis, D. Haritos, V. Boumis, E. Halkia, K. Fragopoulos, E. Efstathiou

1st Dept. of Surgery, Metaxa Cancer Hospital, Piraeus, Greece

ABSTRACT

Aim: The objective of this study was to compare the effectiveness of TachoSil® haemostatic agent in thyroid surgery. **Material and Methods:** Ninety patients who underwent thyroidectomy were included in a prospective study with two arms. All patients were operated on by the same two surgeons (EE, JS). In Group A (45 patients), after the completion of the operation, a TachoSil® haemostatic sponge (Takeda Austria GmbH, Linz, Austria) was placed to cover the thyroid bed. In Group B (45 patients), a TachoSil® haemostatic sponge was not placed at the end of the operation. In all patients, a drain was left behind. **Results:** Mean operation time was reduced in Group A (70 min, vs. 84 min in Group B, p=0.02). Drain fluid collection on the first postoperative day was less in Group A (30 ml, vs. 52 ml in Group B, p<0.003). Drain removal occurred earlier in the TachoSil® group (Group A), resulting in shorter postoperative hospital stay (3.2 days, vs. 4.8 days, p<0.003). **Conclusions:** TachoSil® is an effective agent additional to conventional haemostatic methods in thyroid surgery. Its application reduces operation time, postoperative fluid drainage, time to drain removal and hospital stay.

KEY WORDS: haemostatic agent, thyroid surgery, drain

INTRODUCTION

Thyroidectomy is one of the most commonly performed operations in endocrine surgery. The reported rate of complications is approximately 4.3%, the most common being vocal cord paresis – paralysis, hypoparathyroidism, hypocalcaemia, haemorrhage – haematoma and wound infection.[1]

Haemorrhage and haematoma may require immediate surgical re-exploration, which should be performed in the operating room, unless the airway is compromised. This can be avoided by meticulous haemostasis at closing, which should result in less than 1% occurrence.[2]

Poor haemostasis and a consequent haematoma formation can be attributed to several parameters. Inadequate haemostasis at the time of wound closure can result in a haematoma. Moreover, rough handling of the tissues during the closure can predispose to wound haematomas. Finally, coagulopathies may lead to postoperative haematomas due to clotting factor exhaustion. This can

Correspondence address:
Spiliotis John, MD, PhD. Metaxa Hospital, 51Botassi, 18537 Piraeus, Greece,
Mobile: +30-6942-404014, e-mail: jspil@in.gr

be prevented by correcting clotting abnormalities preoperatively and discontinuing medications that prolong bleeding times.[2]

Adequate haemostasis can be achieved intraoperatively with the additional use of haemostatic agents, such as TachoSil® (Takeda Austria GmbH, Linz, Austria). TachoSil® is a fixed combination of a patch sponge coated with a dry layer of fibrinogen and thrombin. It achieves haemostasis and sealing in 3-5 minutes and it is absorbed by the body within 12 weeks of application.

Regarding the mechanism of action of TachoSil®, initially the sponge's yellow side, which contains the coagulation factors, is applied onto the wound. As the coating dissolves, coagulation factors are released and fibrin generation is initiated. Then the patch structure folds in and leaves an air and liquid tight seal.[3]

The objective of this study was to investigate the effectiveness of TachoSil® as a haemostatic agent in thyroid surgery.

MATERIAL AND METHODS

Over a period of 4 years (2009-2012), our team performed 570 thyroidectomies. Our study population includes 90 of these patients. All patients were operated on by the same surgeons (JS, EE). The patients were divided prospectively in two arms. The first group (A) consists of 45 patients, in whom TachoSil® was placed on the thyroid bed after the thyroidectomy. The second group (B) consists of 45 patients, in whom TachoSil® was not used. A suction drain was placed in the thyroid bed in all patients.

The outcomes measured were operation time, drain fluid collection and hospital stay. Differences in these parameters were studied for statistical significance. Statistic analysis was performed using the Statistical Package for Social Sciences (SPSS) version 21.0 and Microsoft Excel. Differences with a p-value of less than 0.05 were considered statistically significant.

RESULTS

Operation Time

In the TachoSil® group (A), the mean operation time was 70 min. In the group in which TachoSil® was not used (B), the mean operation time was 84 min. This difference was statistically significant (p=0.02, Figure 1).

Drain fluid collection

The mean drain fluid collection on the first postoperative day was 30 ml in the TachoSil® group (A), whereas in the group in which TachoSil® was not used (B), the drain fluid collection was 52 ml, with the difference also being statistically significant (p<0.03, Figure 2)

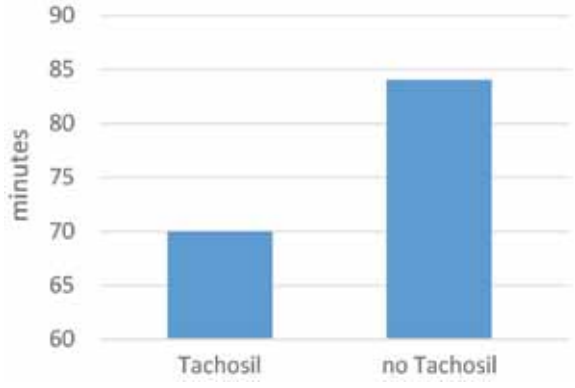

Figure 1. Mean operation time, 70 min vs. 84 min, p=0.02.

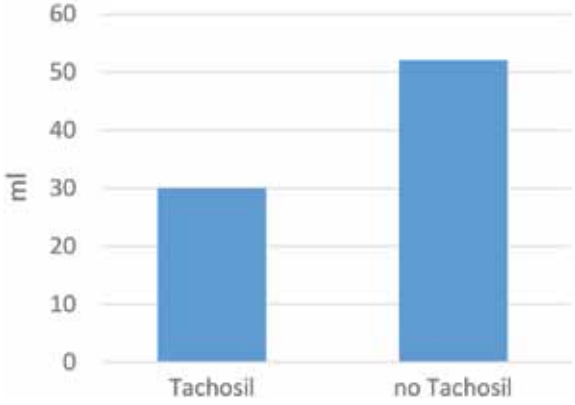

Figure 2. Mean drain fluid collection on the first postoperative day, 30 ml vs. 52 ml, p<0.03.

Hospital stay

The length of hospital stay after thyroid surgery depends on the amount of days the draining tube has to remain. In the TachoSil® group (A), the mean length of postoperative hospitalization was 3.2 days versus 4.8 days in the group in which TachoSil® was not used (B), yielding a statistically significant difference ($p<0.03$, Figure 3).

DISCUSSION

Our study has shown that TachoSil® serves as an effective additional haemostatic measure in thyroid surgery, achieving shorter operation time, reduced drain fluid collection and shorter length of hospital stay.

Achieving adequate haemostasis in thyroid surgery is particularly important, given that haemorrhage or the formation of a haematoma is potentially life-threatening, as it may compress the patient's airway and is a complication that requires prompt surgical intervention.

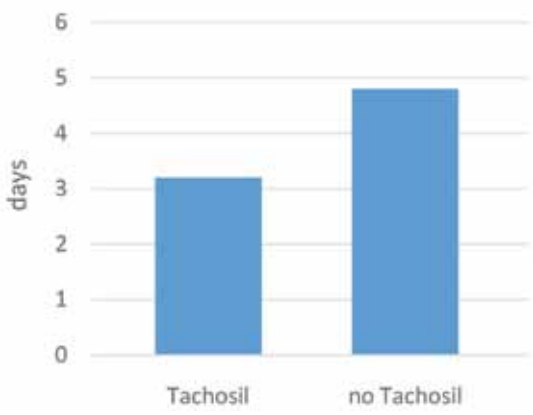

Figure 3. Mean hospital stay, 3.2 days vs. 4.8 days, $p<0.03$.

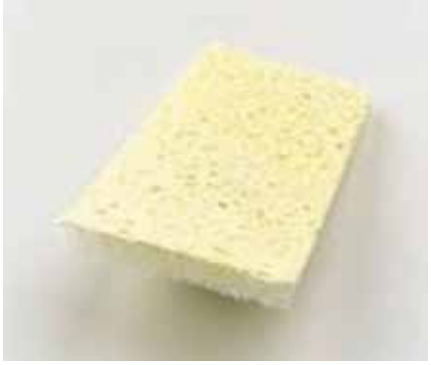

Figure 4. The TachoSil® patch.

Several studies have explored the benefits of using TachoSil® in various surgical procedures. Regarding thyroidectomy complications, Rosato et al[1] reported a case of delayed tracheal laceration due to ischemic damage to the trachea after total thyroidectomy which was managed with both direct sutures of tracheal breaches and the use of TachoSil®, with excellent result.

Erb et al[3] performed a large animal study, in which TachoSil® was used as an additional agent in coronary artery bypass surgery, instead of the placement of additional sutures on the graft. The postoperative result was similar to that of suturing, with patent anastomoses and sufficient bypass flow.[3]

Several authors have reported the efficacy of TachoSil® or its predecessor products in reducing blood loss and achieving haemostasis.[4-6]

The use of TachoSil® in thyroid surgery has been evaluated in the context of a large cohort prospective study (n=482), including 159 patients with disrupted coagulation, assessing parameters such as handling, surgeon satisfaction, utility and pharmacoeconomic benefits, with promising results.[7]

In conclusion, in agreement with previous literature, our study suggests that TachoSil® can be used effectively and safely in thyroid surgery, resulting in an overall better outcome. The use of TachoSil® in thyroid surgery reduces operation time, drain fluid collection and therefore the length of hospitalization, making it an effective additional agent to conventional haemostatic methods in thyroid surgery.

REFERENCES

1. Rosato L, Ginardi A, Mondini G, Sandri A, Oliaro A, Filosso PL. Efficacy of fleece-bound sealing system (TachoSil®) in delayed anterior tracheal lacerations

secondary to ischemic tracheal necrosis after total thyroidectomy. *Minerva Chir* 2012; 67: 271-275.
2. Smith PW, Salomone LJ, Hanks JB. Thyroid. In: Sabiston Textbook of Surgery. The biological basis of modern surgical practice. 19th edition. Townsend CM Jr., Beauchamp RD, Evens BM, Mattox KL (eds). Elsevier Saunders, Philadelphia 2012; pages 886-923.
3. Erb MA, Claus T, Hartrumpf M, Bachmann S, Albes JM. The use of TachoSil® surgical patch or fibrin glue in coronary artery surgery does not affect quality of anastomosis or provoke postoperative adhesions in pigs. *Eur J Cardiothorac Surg* 2009; 36: 703-707.
4. Lang G, Csekeö A, Stamatis G, et al. Efficacy and safety of topical application of human fibrinogen/thrombin-coated collagen patch (TachoComb) for treatment of air leakage after standard lobectomy. *Eur J Cardiothorac Surg* 2004; 25: 160-166.
5. Joseph T, Adeosun A, Paes T, Bahal V. Randomised controlled trial to evaluate the efficacy of TachoComb H patches in controlling PTFE suture – hole bleeding. *Eur J Endovasc Surg* 2004; 27: 549-552.
6. Schwaitzberg SD, Chan MW, Cole DJ, et al. Comparison of poly-N-acetyl glucosamine with commercially available topical hemostats for achieving hemostasis in coagulopathic models of splenic hemorrhage. *J Trauma* 2004; 57(1 Suppl): S29-S32.
7. Non-Interventional study about treatment of hemorrhages in hhyroid surgery with TachoSil®. http://www.takeda.com/research/ct/files/TC-9999-036-BE-RDS-2013-12-12.pdf. Accesses October 16, 2014.

HELLENIC SURGICAL ONCOLOGY 2014; 5(2): 84-93

ORIGINAL PAPER

The management of desmoid tumours
Experience of a single centre during the last 10 years

E. de Bree,[1] S. Kachris,[2] M. Papadakis,[3] D. Michelakis,[1] V. Lamprou,[1] M. Christodoulakis,[1] A. Karantanas,[4] O. Zoras[1]

[1]Melanoma and Sarcoma Unit, Department of Surgical Oncology, [2]Department of Radiotherapy and Oncology, [3]Department of Pathology, [4]Department of Medical Imaging, Medical School of Crete University Hospital, Heraklion, Greece

ABSTRACT

Aim: Desmoid tumour is a rare and heterogeneous disease with many treatment options. It requires individualized management to achieve local tumour control without increase of morbidity and function loss. Treatment modalities include surgery, radiotherapy, systemic treatment and a wait-and-see policy. The aim of the present study was to analyse the treatment of desmoid tumours in our unit. Material and Methods: The archives of our unit were studied to identify patients treated for desmoid tumours during the last 10 years. The patients' characteristics, tumour localization size and site and treatment were recorded. Results: Eight patients, 7 women and 1 man, were identified to have been treated for a desmoid tumour in our unit from 2004 to 2013. Their median age was 35 years (range 30-63, mean 41). Seven patients presented with a primary tumour and one patient with a local recurrence. The tumour was located in the abdominal wall (n=4), in the mesentery/mesocolon (n=3) and in the lumbar region (n=1). The tumour size varied from 2 to 33 cm (median 5.5 cm, mean 10 cm). After a median follow up of 64 months (mean 58 months, range 11-122 months) local recurrence had occurred in 1 of the 7 (14%) patients that had undergone surgery for their desmoid tumour. The local recurrence was treated with surgery and adjuvant radiotherapy, resulting in local tumour control during 42 months of follow-up. Stable tumour size was achieved in the elderly patient for 18 months with the administration of indomethacin and tamoxifen. No long-term morbidity had been noted. Conclusions: Desmoid tumours require individualized management to achieve local tumour control without increase of morbidity or function loss. In our small series, adequate local tumour control was achieved with surgery, with or without radiotherapy, and medical treatment.

Key words: desmoid, aggressive fibromatosis, desmoid-type fibromatosis, treatment, multimodality treatment, surgery, radiotherapy

INTRODUCTION

Desmoid tumour, also called aggressive fibromatosis because of its more aggressive type of growth, is a benign proliferative disease of fibrous tissue origin.[1] Although histologically benign, desmoids are often locally invasive and associated with a high local recurrence rate after resection.[1,2]

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

Desmoid tumours are rare, comprising 0.03% of all neoplasms and 3% of all soft tissue tumours. The estimated incidence in the general population is 2 to 4 per million citizens per year.[3] They usually occur sporadically, but approximately 5% are associated with familial adenomatous polyposis (FAP) in Gardner syndrome. The term desmoid was first used by Müller[4] to denote tumours of varying consistency, usually firm and tendon-like, and derives from the Greek word 'desmos', meaning tendon.

This fibroblastic disorder may be observed in nearly every part of the body. Although numerous sites have been identified, desmoids occur most commonly in extremities (mostly limb girdles and proximal extremities).[5] Most patients with abdominal wall involvement are females during or after pregnancy. In Gardner syndrome, desmoids are most often located in the abdomen and less often in the abdominal wall.[6,7]

Although computed tomography may be valuable, especially for intra-abdominal locations, magnetic resonance imaging is the imaging modality of choice for diagnosis, evaluation of the tumours' extent and follow-up examination.[8] The main clinical differential diagnosis comprises soft tissue sarcoma, (extranodal) lymphoma, myositis ossificans and arteriovenous malformation. Imaging is usually able to adequately exclude the latter diseases, but differentiation between desmoids and malignant sarcoma often remains difficult.[8] In these cases, the use of FDG-PET could be of help; desmoid tumours show a low level of tracer uptake, being the described maximum standardized uptake values (SUV) in general lower than 4, whereas malignant diseases show higher values.[9] Final diagnosis is established by histology. Preoperative diagnosis by Tru-cut biopsy or incisional biopsy is advocated. Differential diagnosis at histology includes fibrosarcoma, low-grade fibromyxoid sarcoma, low-grade leiomyosarcoma, gastrointestinal stromal tumours, reactive fibroblastic proliferations, desmoplastic fibroma, myxoma, and nodular fascitis.[5,10]

The optimal treatment of this tumour remains difficult to determine.[2,11,12] Assessment of efficacy of various treatment modalities is complicated by the rarity and the heterogeneity of the disease. Large or randomized series do not exist to appropriately assess the impact of various treatment modalities that are used. Assessment of treatment response is also complicated by the very unpredictable natural history of desmoid tumours. Therapy consists of surgery, radiotherapy, and/or systemic approaches in various non-standardized combinations, rendering direct comparison of treatment results problematic.[2] Furthermore, desmoid tumours occur at various anatomical sites, which may require different treatment, making meaningful conclusions difficult to reach due to lack of comparability.

We reviewed the management of desmoid tumours in the Melanoma and Sarcoma Unit of the Department of Surgical Oncology of the Medical School of Crete University Hospital in Greece over a ten year period.

PATIENTS AND METHODS

The archives of the Melanoma and Sarcoma Unit of the Department of Surgical Oncology of the Medical School of Crete University Hospital were studied to identify patients treated for desmoid tumours during the last 10 years. The patients' characteristics, tumour localization size and site and treatment were recorded. Special attention was paid to the management of each tumour.

The patients were regularly seen at the outpatient clinic, usually every 3 months during the first 2 years, bi-annually for another 3 years and then on annually. Evaluation included patient's history, physical examination and bi-annual or annual magnetic resonance imaging of the area of interest.

RESULTS

Eight patients, 7 women and 1 man, were iden-

tified to have been treated for a desmoid tumour in our unit from 2004 to 2013. Their median age was 35 years (range 30-63, mean 41). In all patients histological examination had provided the diagnosis of a desmoid tumour. Seven patients presented with a primary tumour and one patient with a local recurrence 6 months after initial surgery elsewhere. In four female patients, including the patient who presented to us with a recurrence, the tumour was located in the abdominal wall, in three female patients the tumour originated from the mesentery/mesocolon and in the male patient the tumour was found in the lumbar region. The tumour size varied from 2 to 33 cm (median 5.5 cm, mean 10 cm). Regarding the potential aetiological factors, three female patients, two with tumour location in the abdominal wall and one with an intra-abdominal desmoid tumour, had a recent history of pregnancy. None of the patients had a history of trauma or FAP.

Two of the three patients with a primary desmoid tumour located in the rectus abdominis muscle, 2.5 and 4 cm in size, and one patient with a recurrent desmoid tumour located in the rectus abdominis muscle, 2 cm in size, underwent wide local excision of the tumour, with full thickness removal of the muscular abdominal wall and peritoneum (Figure 1). In all cases, a mesh was used for abdominal wall reconstruction. The surgical margins were free of tumour cell in all cases. None of the patients underwent adjuvant treatment. The patients were free of recurrence respectively 78, 64 and 11 months after surgery. No long-term morbidity or function loss had been noted. An 86-year old female patient presented with an 11.5 cm tumour of the upper abdominal wall (Figure 2). Core needle biopsy demonstrated histological features of a desmoid tumour. Taking into account of the indolent growth of the female patient's tumour before presentation, the extent

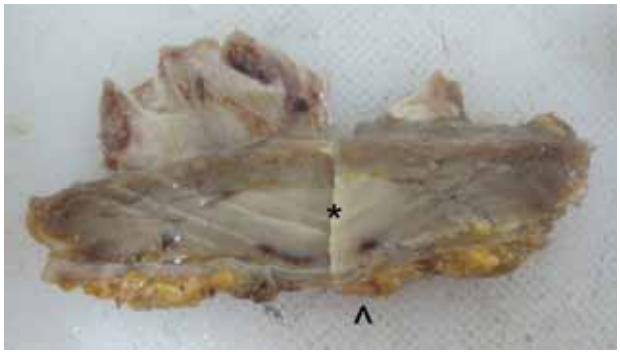

Figure 1. Surgical specimen of full thickness excision of the muscular abdominal wall and peritoneum for a desmoid tumour located in the rectus abdominis muscle. Note the lack of circumscribed borders of the whitish tumour (*). The resection included the deep layer of the rectus abdominis sheath and the peritoneum with its peritoneal fat (^).

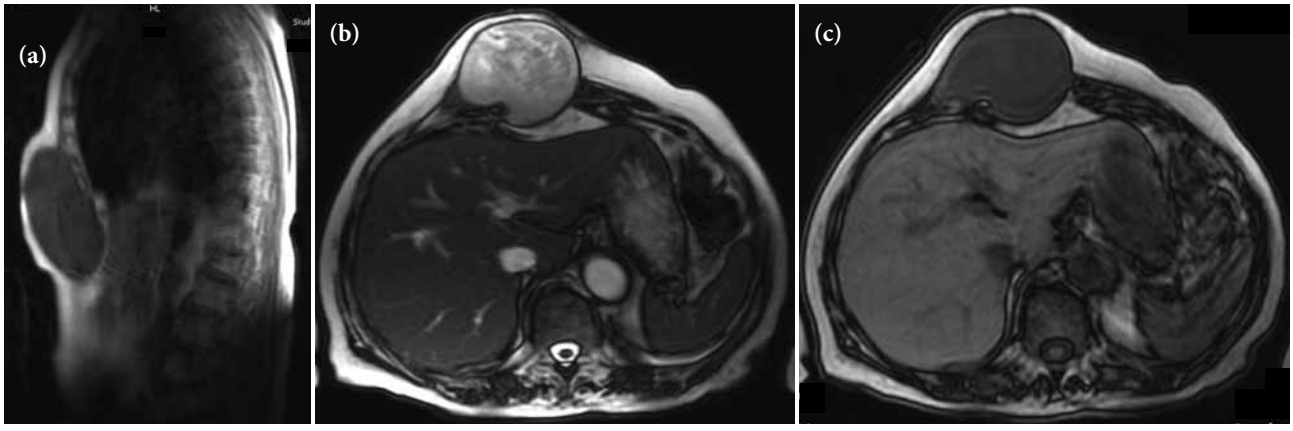

Figure 2. A 86-year-old female patient with a large desmoid tumour in the rectus abdominus muscle. The sagittal T1-w (a), axial T1-w (b) and axial True FISP T2-w (c), MR images, show the large lesion in the anterior abdominal wall, exhibiting low signal intensity on T1-w and inhomogenously high signal intensity on T2-w images.

of the surgical procedure needed for eventual removal of the tumour, as well as the her age and co-morbidities, she was not operated on but treated with indomethacin (150 mg daily p.o.) and tamoxifen (20 mg daily p.o.). Eighteen months after initiation of the medical treatment, the tumour remained stable in size.

The three patients with desmoid tumours, 9, 11.5 and 33 cm in size, originating from the mesentery or mesocolon underwent en block bowel resections. In the patient with a 33 cm large and 6.2 kg weighted intra-abdominal desmoid tumour, a wide rim of the pancreas also had to be resected because of tumour infiltration. The latter case has been described in detail elsewhere.[13] In all three cases, the tumour appeared to have been completely resected and no adjuvant treatment had been administered. After 122, 52 and 67 months, respectively, the tumours had not recurred. No long-term morbidity or function loss had been observed.

The male patient with a desmoid tumour in the lumbar region underwent resection of desmoid tumour with a maximal diameter of 5.5 cm (Figure 3). Despite microscopically negative surgical margins the tumour recurred after 14 months. He underwent a microscopically complete resection of the recurrence and adjuvant radiotherapy (50 Gy in 25 fractions). Forty-two months after excision of the local recurrence there are no signs of re-recurrence. No long-term morbidity or function loss has been noted.

In conclusion, local recurrence had occurred in 1 of the 7 (14%) patients that had undergone surgery for their desmoid tumour after a median follow up of 64 months (mean 58 months, range

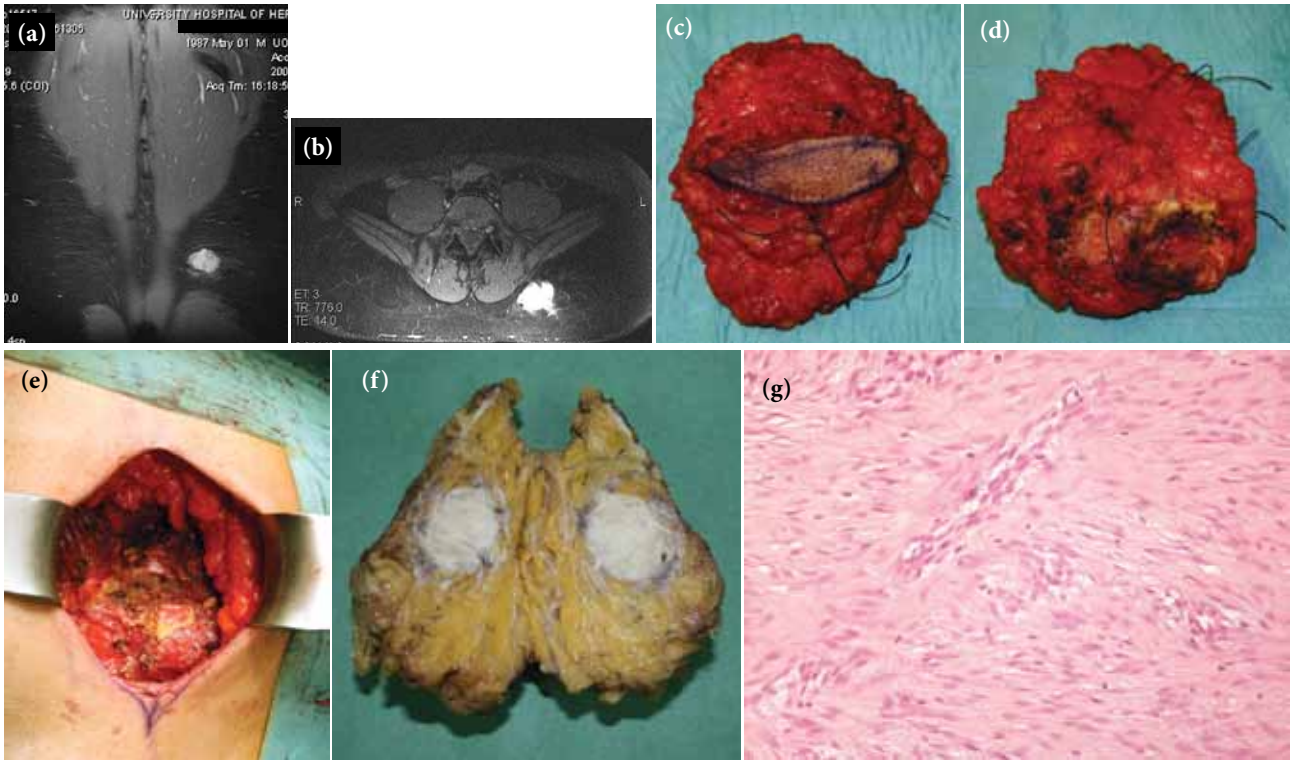

Figure 3. Desmoid tumour in the lumbar region of a 22-year old male patient. The coronal STIR (a) and contrast enhanced fat suppressed axial T1-w (b) MR images, show a high signal intensity lesion with intense and homogenous enhancement respectively, located in the subcutaneous tissue. Fresh specimen of the tumour covered by macroscopically normal tissue (c,d).The bed of the surgical excision, macroscopically free of disease (e). Dissection of the tumour after fixation in formaldehyde, demonstrating its infiltrative growth (f). Histological examination of the desmoid tumour (g).

11-122 months). The local recurrence was treated with surgery and adjuvant radiotherapy, resulting in local tumour control during 42 months of follow-up. Stable tumour size was achieved in the elderly patient for 18 months with the administration of indomethacin and tamoxifen. No treatment-related long-term morbidity or function loss had been observed.

DISCUSSION

Comprehension of their biological behaviour and natural history, as well as knowledge of aetiological factors and pathogenesis is essential for therapeutic management of desmoid tumours. Numerous factors are acknowledged to be strongly associated with their development. Increased incidence during and after pregnancy and following exposure to oral contraceptives, preponderance of cases afflicting women of reproductive age in many series, anecdotal reports of spontaneous tumour regression during menopause and reports of tumour regression with tamoxifen treatment underline the influence of the female sex hormonal environment.[2,3] An antecedent history of trauma to the site of the tumour, often surgical in nature, may be elicited.[2,3,14] Desmoid tumours have been associated with hereditary syndromes, such as in Gardner syndrome. The incidence of desmoids in FAP has been estimated to be around 850 times higher than that of the general population.[15] It seems that the location of mutations within the APC gene determines the propensity for desmoid tumor development on top of the classic FAP phenotype of colonic polyps and cancer.[14] Whereas desmoid development is linked to germ-line inactivating mutations of the APC gene in FAP patients,[14] patients with sporadic desmoids usually harbour somatic beta-catenin activating mutations.[16,17] Because APC and beta-catenin are both members of the WNT pathway, one may suggest that this pathway is altered in all desmoids, irrespective of familial and sporadic origin. These mutations may cause activation of cyclooxygenase-2 (COX-2) which in desmoid tumours seems to modulate fibroblast proliferation by increasing the expression of growth factors such as platelet-derived growth factors (PDGF).[18-21] Among various other effects, beta-catenin can regulate matrix metalloproteinase (MMP) activity, which seems to play a crucial role in regulating the invasiveness of mesenchymal cells and in modulating aggressive fibromatosis tumour progression.[21,22] the above mentioned factors such as female sex hormone receptors, COX-2, PDGF and MMP may be specifically targeted with medical treatment.[21]

Although histologically benign, they exhibit locally malignant behaviour and are notorious for a high incidence of local recurrence. Local infiltrative growth may result in significant morbidity. Desmoids do not have a capsule, infiltrate along fascial planes, and may invade adjacent neurovascular structures. Its natural history is unpredictable. Despite its lack of metastatic potential, this as histologically benign classified tumour may, although rarely, eventually lead to death because of its locally aggressive and progressive nature, especially when located in the abdomen at sites not amenable to wide resection.[6,10] On the other hand, spontaneous regression and enduring stable disease in the absence of treatment have been reported.[23-25] While complete spontaneous regression is probably very rare, prolonged disease stabilization with tumours undergoing cycles of growth and resolution in the absence of any attempted treatment is more frequently observed.

Treatment has changed from surgery as a single option to a multimodality approach.[26] Surgery and radiotherapy are most commonly applied in the treatment of desmoid tumours, while systemic treatment modalities are usually only used in the case of inoperable lesions, especially when localized intra-abdominally, and in the case of failure after surgery and/or radiotherapy.[2,26] Systemic treatment includes administration of anti-inflammatory agents, hormonal therapy, chemotherapy and molecular-based treatment. In selected cases, observation with only a wait-and-see policy might

be indicated.[2,26] Treatment of recurrent tumours is not essentially different than that of primary desmoids, but management may be more difficult and, depending on its location, repeated surgery may be associated with increased functional impairment.

Surgical resection with negative margins is the treatment of choice for primary and recurrent desmoid tumours.[2,5,11,12] Partial gross resection should be avoided and alternative treatment modalities should be considered, because surgery may trigger rapid tumour progression. To achieve tumour free margins macroscopically, wide excision of the tumour is indicated, due to its lack of capsule and infiltrative growth. Although the principal objective is to obtain microscopically tumour free surgical margins, local recurrences may occur even after an appropriate wide resection, while in a substantial number of patients with involved surgical margins local recurrence does not arise.[2,5,27] Despite conflicting data in reports regarding the association between microscopic surgical margins and risk of local recurrence,[2,28] in three large comparative analyses[11,29,30] of multiple studies, their status was a highly significant prognostic factor for local recurrence. In patients treated with surgery only, involvement of surgical margins diminished local control rates significantly (p=0.008) from 70% to 46% for primary tumours and from 71% to 18% for recurrences, when compared with adequate resections.[29] The low local recurrence rate in our small series (14%) may be attributed to the fact that the surgical margins were all microscopically free of disease. We did not observe treatment related long-term morbidity or function loss. Although the margin status is of importance, operations that preserve function and structure should be the primary goal.[2] Attempts to achieve negative margins may result in unnecessary morbidity and may not definitely prevent local recurrence, whereas positive surgical margins do not always result in local recurrence and desmoid tumours may remain stable in size for a prolonged period of time or even regress spontaneously.[2,31-33] Resections that might be mutilating, are associated with considerable function loss or major morbidity or cause disfigurement should be avoided when possible.[2,34] This is especially the case in areas with delicate structures and anatomical constraints, as for example in the head and neck region.[35] the consequences of radical excision may be worse than the disease itself. Surgery, with or without radiotherapy, is the most reasonable treatment option for patients with desmoid tumours whose surgical morbidity is deemed to be low.[12] In some instances, radiotherapy can be administered, either on its own or after conservative surgery, without major compromise in local control.[28-30]

The application of radiotherapy has been extensively debated, given the fact that desmoid disease is a benign condition and complications, although usually mild or moderate and location and radiation dose dependent, occur relatively frequently. Radiotherapy has been used as adjuvant treatment, as in other forms of fibromatosis,[36] and as primary treatment.[37] Because of its toxicity, radiotherapy is mainly administered for extra-abdominal desmoid tumours. The decision as to whether radiotherapy should be offered in conjunction with surgery should be made by clinicians and patients after weighing the potential benefit of improved local control against the potential harms and toxicity associated with radiotherapy.[11,12] The addition of radiotherapy after surgery was an independent positive prognostic factor in an international survey study.[38] As adjuvant treatment, it has commonly been used in cases of positive surgical margins and after surgery for recurrent tumours in an attempt to decrease the risk of local recurrence.[37] In a comparative review of 22 articles and including 780 patients,[29] the addition of radiotherapy to surgery increased the local tumour control rate from 47% to 79% (p=0.00002) in recurrent tumours and, much less dramatically, from 62% to 78% (p=0.027) in primary tumours. In case of positive surgical margins, postoperative radiotherapy improved local disease control dramatically to a level similar to that of complete resection: from

46% to 78% (p=0.0001) in primary and from 18% to 76% ($p=6 \times 10^{-8}$) in recurrent desmoids.[29] In cases of tumour free surgical margins, the benefit of adjuvant radiotherapy was small and statistically non-significant, and should be weighed against its complications.[29] In our series, adjuvant radiotherapy had only been used in a young male patient after excision of a local recurrence which occurred 14 months after primary surgery. Forty-two months later, he is still free of re-recurrence. As primary treatment radiotherapy might be indicated in inoperable or inaccessible disease and to avoid mutilating surgery. Primary radiotherapy for gross disease appears very effective in local control of the tumour.[39] However, local tumour control most frequently reflects stable disease or size reduction and does not usually result in eradication of the disease. Response after radiation therapy is slow, with continuing regression seen in some cases even after a 3 year time period has transpired.[39]

Treatment with various drugs has been attempted for patients with desmoid tumours that are not amenable to surgery or radiotherapy, with some success.[11,40,41] Noncytotoxic and cytotoxic systemic therapy has been used for inoperable and unresectable tumours, to avoid radiotherapy or surgery related significant morbidity and/or function loss, for residual and progressive disease after initial local treatment, and in rare cases, as induction treatment to facilitate wide surgical resection.[40,42] Because of the observation of effectiveness in some cases and their low toxicity, endocrine and NSAID therapy has usually been considered first-line medical treatment.[40,43] As discussed above, their effectiveness is based respectively on inhibition of cyclooxygenase, which seems to play a key role in the pathogenesis of desmoid tumours, and the potential hormonal influence on desmoid tumour growth. In our elderly patient with a locally advanced desmoid tumour, the size remained stable during treatment with this drug combination. In children, however, the activity of this drug combination seems to be considerably limited.[44] Although most desmoids are c-Kit negative, there is a rational to also treat these cases with imatinib mesylate, since studies have demonstrated that PDGF receptors are consistently activated in these tumours.[20,45] In multicenter trials, responses of desmoid tumours to therapy with the tyrosine kinase inhibitor imatinib mesylate have been reported.[46-48] Most recently, activity of the second-line tyrosine kinase inhibitor sorafenib against progressive desmoid tumours has been reported.[49] Additionally, various cytotoxic drug combinations have been used with varying success.[11,41,42,50,51] A recent multicentre study demonstrated that isolated limb perfusion using tumour necrosis factor α and melphalan is effective in patients with advanced desmoid tumours of the limbs.[52]

In selected patients with unresectable disease, or when eventual resection is associated with high morbidity, a period of watchful waiting until significant symptoms develop or the tumour progresses may compose the most appropriate management when bearing in mind the natural history of desmoid tumours, which is often characterized by prolonged periods of stability or even regression.[23,24,32] A period of careful observation may demonstrate the tumour's natural behaviour, when this has not been clear from the patient's history. When the disease is stable, observation may be appropriate for a long duration. However, treatment is indicated in cases of progressive or symptomatic disease. Since it is a variable disease with several different clinical entities existing within the same label, the final decision of whether or not to treat desmoid tumours that are inoperable or inaccessible, for which surgical resection or radiation is mutilating or associated with substantial morbidity, or which recur or progress after initial treatment, should be a rational one based on patient characteristics, symptoms and the biological properties of the tumour.[23,24,32,33,53] Observation does not seem to have a negative impact on tumour control in selected patients who have desmoids with relatively favourable biological behaviour.[23]

After treatment, evaluation for rehabilitation, occupational therapy and/or physical therapy, is recommended. Rehabilitation should be continued until maximal function is achieved. Follow-up examinations including history and physical examinations with appropriate imaging are recommended every 3-6 months for 2-3 years, and then on annually.[12] Our patients were monitored in quite a similar way.

From the above mentioned it is obvious that this rare and heterogeneous disease requires individualized management to achieve local tumour control without increase of morbidity or function loss. Treatment has changed from surgery as a single option to a multimodality approach. In our small series, adequate local tumour control was achieved with surgery, with or without radiotherapy, and medical treatment, while no long-term morbidity or function loss was observed. In view of the potentially complex management of this rare tumour, treatment in referral centres has to be encouraged. Similarly to management of malignant soft tissue tumours in referral centres, this will most probably lead to improved outcome.[54]

ACKNOWLEDGEMENT

We would like to thank Mrs. Eugenia Bolbasis for the linguistic review of this manuscript.

REFERENCES

1. Enzinger FM, Weiss SW. Fibromatosis. In: Enzinger FM, Weiss SW (eds) Soft tissue tumours. 5th Edition. Mosby Inc., St. Louis 2008; 227-253.
2. de Bree E, Keus R, Melissas J, Tsiftsis DD, van Coevorden F. Desmoid tumors: need for an individualized approach. *Expert Rev Anticancer Ther* 2009; 9: 525–535.
3. Reitamo JJ, Scheinin TM, Hayry P. The desmoid syndrome: new aspects in the cause, pathogenesis and treatment of the desmoid tumor. *Am J Surg* 1986; 151: 230-237.
4. Muller J. Über den feinern bau und die formen der krankenhaften geschwulste. Berlin: G. Reimer, 1838: 1-60.
5. Papagelopoulos PJ, Mavrogenis AF, Mitsiokapa EA, et al. Current trends in the management of extra-abdominal desmoid tumours. *World J Surg Oncol* 2006; 4: 21.
6. Sakorafas GH, Nissotakis C, Peros G. Abdominal desmoid tumors. *Surg Oncol* 2007; 16: 131-142.
7. Levefre JH, Parc Y, Kerneis S, et al. Risk factors for development of desmoid tumours in familial adenomatous polyposis. *Br J Surg* 2008; 95: 1136-1139.
8. Lee JC, Thomas JR, Phillips S, et al. Aggressive fibromatosis: MRI features with pathologic correlation. *Am J Roentgenol* 2006; 186: 274-254.
9. Basu S, Nair N, Banavali S. Uptake characteristics of fluorodeoxyglucose (FDG) in deep fibromatosis and abdominal desmoids: potential clinical role of FDG-PET in the management. *Br J Radiol* 2007; 80: 750-756.
10. Mendenhall WM, Zlotecki RA, Morris CG, et al. Aggressive fibromatosis. Am J Clin Oncol 2005; 28: 211-215.
11. Yao X, Corbett T, Gupta AA, et al. A systematic review of active treatment options in patients with desmoid tumours. *Curr Oncol* 2014; 21: e613-e629.
12. Ghert M, Yao X, Corbett T, et al. Treatment and follow-up strategies in desmoid tumours: a practice guideline. *Curr Oncol* 2014; 21: e642-e649.
13. de Bree E, Dimitriadis E, Giannikaki E, Chryssou EG, Melissas J. A giant pregnancy-associated intra-abdominal desmoid tumour: not necessarily a contraindication for subsequent pregnancy. *World J Surg Oncol* 2013; 11: 277.
14. Nieuwenhuis MH, Lefevre JH, Bülow S, et al. Family history, surgery, and APC mutation are risk factors for desmoid tumors in familial adenomatous polyposis: an international cohort study. *Dis Colon Rectum* 2011; 54: 1229-1234.
15. Nieuwenhuis MH, de Vos tot Nederveen Cappel W, Botma A et al. Desmoid tumors in a Dutch cohort of patients with familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2008; 6: 215-219.
16. Tejpar S, Nollet F, Li C, et al. Predominance of beta-catenin mutations and beta-catenin dysregulation in sporadic aggressive fibromatosis (desmoid tumor). *Oncogene* 1999; 18: 6615-6620.
17. Li C, Bapat B, Alman BA. Adenomatous polyposis coli gene mutation alters proliferation though catenin regulatory function in aggressive fibromatosis (desmoid tumour). *Am J Pathol* 1998; 153: 709-714.
18. Cheon SS, Cheah AY, Turley S, et al. Beta-catenin

stabilization dysregulates mesenchymal cell proliferation, motility, and invasiveness and causes aggressive fibromatosis and hyperplastic cutaneous wounds. *Proc Natl Acad Sci U S A* 2002; 99: 6973-6978.
19. Poon R, Smits R, Li C, et al. Cyclooxygenase-two (COX-2) modulates proliferation in aggressive fibromatosis (desmoid tumor). *Oncogene* 2001; 20: 451-460.
20. Signori S, Frattinin M, Negri T, et al. Cyclooxygenase-2 and platelet-derived growth factor receptors as potential targets in treating aggressive fibromatosis. *Clin Cancer Res* 2007; 13: 5034-5040.
21. Kotiligam D, Lazae AJ, Pollock RE, Lev D. Desmoid tumor: a disease opportune for molecular insights. *Histol Histopathol* 2008; 23: 117-126.
22. Kong Y, Poon R, Nadesan P, et al. Matrix metalloproteinase activity modulates tumor size, cell motility, and cell invasiveness in murine aggressive fibromatosis. *Cancer Res* 2004; 64: 5795-5803.
23. Bonvalot S, Eldweny H, Haddad V, et al. Extra-abdominal primary fibromatosis: Aggressive management could be avoided in a subgroup of patients. *Eur J Surg Oncol* 2008; 34: 462-468.
24. Bertagnolli MM, Morgan JA, Fletcher CDM, et al. Multimodality treatment of mesenteric desmoid tumors. *Eur J Cancer* 2008; 44: 2404-2410.
25. Church JM. Desmoid tumors in patients with familial adenomatous polyposis. *Semin Colon Rectal Surg* 1995; 6: 29-32.
26. Lev D, Kotilingam D, Wei C, et al. Optimizing treatment of desmoid tumors. *J Clin Oncol* 2007; 25: 1785-1791.
27. de Bree E, van Coevorden F, Keus RB, Tsiftsis DD. Treatment of extremity desmoid tumours. *Eur J Surg Oncol* 2004; 30: 1141-1142.
28. Melis M, Zagar JS, Sondak VK. Multimodality management of desmoid tumors: How important is a negative surgical margin? *J Surg Oncol* 2008; 98: 594-602.
29. Nuyttens JJ, Rust PF, Thomas CR Jr, Turrisi AT III. Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors. A comparative review of 22 articles. *Cancer* 2000; 88: 1517-1523.
30. Leithner A, Gapp M, Leithner K, et al. Margins in extra-abdominal desmoids tumors: A comparative analysis. *J Surg Oncol* 2004; 86: 152-156.
31. Merchant NB, Lewis JJ, Woodruff JM, et al. Extremity and trunk desmoid tumors. A multifactorial analysis of outcome. *Cancer* 1999; 86: 2045-2052.
32. Lewis JJ, Boland PJ, Leung DHY, Woodruff JM, Brennan MF. The enigma of desmoid tumors. *Ann Surg* 1999; 229: 866-872.
33. Salas S, Dufresne A, Blay J-Y, et al. Prognostic factors influencing progression-free survival determined from a series of sporadic desmoid tumors: a wait-and-see policy according to tumor presentation. *J Clin Oncol* 2011; 29: 3553-3558.
34. Gronchi A, Casali PG, Mariani L, et al. Quality of surgery and outcome in extra-abdominal aggressive fibromatosis: a series of patients surgically treated at a single institution. J Clin Oncol 2003; 21: 1390-1397.
35. de Bree E, Zoras O, Hunt JL, et al. Desmoid tumors of the head and neck: A therapeutic challenge. *Head Neck* 2014; 36: 1517-1526.
36. de Bree E, Zoetmulder FAN, Keus RB, et al. Plantar fibromatosis: incidence and treatment of recurrences by surgery and postoperative radiotherapy. *Am J Surg* 2004; 187: 33-38.
37. Guadagnolo BA, Zagars GK, Ballo MT. Long-term outcomes for desmoid tumors treated with radiation therapy. *Int J Radiat Oncol Biol Phys* 2008; 71: 441-447.
38. Baumert BG, Spahr MO, von Hochstetter A, et al. The impact of radiotherapy in the treatment of desmoid tumours. An international survey of 110 patients. A study of the Rare Cancer Network. *Radiation Oncology* 2007; 2: 12.
39. Keus RB, Nout RA, Blay JY, et al. Results of a phase II pilot study of moderate dose radiotherapy for inoperable desmoid-type fibromatosis--an EORTC STBSG and ROG study (EORTC 62991-22998). *Ann Oncol* 2013; 24: 2672-2676.
40. Janinis J, Patriki M, Vini L, Aravantinos G, Whelan JS. The pharmacological treatment of aggressive fibromatosis: a systemic review. *Ann Oncol* 2003; 14: 181-190.
41. Kasper B, Ströbel P, Hohenberger P. Desmoid tumors: clinical features and treatment options for advanced disease. *Oncologist* 2011; 16: 682-693.
42. Okuno SH, Edmonson JH. Combination chemotherapy for desmoid tumors. *Cancer* 2003; 97: 1134-1135.
43. Hansmann A, Adolph C, Vogel T, Unger A, Moeslein G. High-dose tamoxifen and sulindac as first-line treatment for desmoid tumors. *Cancer* 2004; 100: 612-620.
44. Skapek SX, Anderson JR, Hill DA, et al. Safety and efficacy of high-dose tamoxifen and sulindac for desmoid tumor in children: Results of a Children's

Oncology Group (COG) Phase II Study. *Pediatr Blood Cancer* 2013; 60: 1108-1112.
45. Liegl B, Leithner A, Bauernhofer T et al. Immunohistochemical and mutational analysis of PDGF and PDGFR in desmoid tumours: is there a role for tyrosine kinase inhibitors in c-kit-negative desmoid tumours? *Histopathology* 2006; 49: 576-581.
46. Penel N, Le Cesne A, Bui N, et al. Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): an FNCLCC/French Sarcoma Group phase II trial with a long-term follow-up. *Ann Oncol* 2011; 22: 452-457.
47. Heinrich MC, McArthur GA, Demetri GD, et al. Clinical and molecular studies of the effect of Imatinib on advanced aggressive fibromatosis (desmoid tumor). *J Clin Oncol* 2006; 24: 1195-1203.
48. Chugh R, Wathen JK, Patel SR, et al. Efficacy of imatinib in aggressive fibromatosis: Results of a phase II multicenter Sarcoma Alliance for Research through Collaboration (SARC) trial. *Clin Cancer Res* 2010; 16: 4884-4891.
49. Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity of Sorafenib against desmoid tumor/deep fibromatosis. *Clin Cancer Res* 2011; 17: 4082-4090.
50. de Camargo VP, Keohan ML, D'Adamo DR, et al. Clinical outcomes of systemic therapy for patients with deep fibromatosis (desmoid tumor). *Cancer* 2010; 116: 2258-2265.
51. Constantinidou A, Jones RL, Scurr M, Al-Muderis O, Judson I. Advanced aggressive fibromatosis: Effective palliation with chemotherapy. *Acta Oncol* 2011; 50: 455-461.
52. van Broekhoven DL, Deroose JP, Bonvalot S, et al. Isolated limb perfusion using tumour necrosis factor α and melphalan in patients with advanced aggressive fibromatosis. *Br J Surg 2014*, Epub ahead of print.
53. Stoeckle E, Coindre JM, Longy M, et al. A critical analysis of treatment strategies in desmoid tumours: a review of a series of 106 patients. *Eur J Surg Oncol* 2009; 35: 129-134.
54. Gutierez JC, Perez EA, Moffat FL, et al. Should soft tissue sarcomas be treated at high-volume centres? An analysis of 4205 patients. *Ann Surg* 2007; 245: 952-958.

HELLENIC SURGICAL ONCOLOGY 2014; 5(2): 94-98

CASE REPORT

Retroperitoneal emphysema and intraabdominal free air following transanal endoscopic microsurgery
Report of a case

D. Stamatiou,[1] V. Charalampakis,[1] M. Christodoulakis[1,2]

[1]*Department of Surgical Oncology, Medical School of Crete University Hospital, Heraklion, Greece,*
[2]*Department of Surgery, Venezeleio General Hospital, Heraklion, Greece*

ABSTRACT

Transanal endoscopic microsurgery (TEM), a minimally invasive procedure for the excision of rectal lesions, is characterized by less morbidity compared to traditional rectal surgical operations with major postoperative complications being peritoneal perforation and bleeding. Herein, we report on a 70-year old patient with a history of previous laparotomies, who developed intra-abdominal free air depicted on chest and abdominal X-ray, accompanied with dyspnoea and hypercapnia, following TEM operation for a large rectal adenoma. The patient underwent emergent laparotomy. Extensive retroperitoneal and mesenterial emphysema were observed, but no peritoneal defect. It is speculated that CO_2 that escapes into the retroperitoneum during the procedure, can diffuse into the intraperitoneal cavity, present as free intraabdominal air, and be misinterpreted as rectal perforation. Since the latter is a serious complication requiring immediate surgery, correct differential diagnosis sis imperative. Computed tomography, diagnostic laparoscopy and watchful waiting have been proposed as means of diagnosis. Conservative treatment can only be considered in stable patients, provided they are free of abdominal symptoms. Since hypercapnia can prove to be a serious complication after TEM, prolonged observation in the recovery room should be offered.

Key words: Transanal endoscopic microsurgery, retroperitoneal emphysema, mesenteric emphysema, free intraabdominal air

INTRODUCTION

Transanal endoscopic microsurgery (TEM) has emerged as a minimally invasive procedure for the treatment of rectal neoplasms.[1] Introduced in the early 1980's as a resection technique for benign rectal adenomas,[2] it offers unique stereoscopic view and exposure, which, combined with the use of both hands of the operator, facilitates precise excision.[1] TEM nowadays is considered

Correspondence address:
D. Stamatiou, MD, Department of Surgical Oncology, University Hospital, P.O. Box 1352, 71110 Heraklion, Crete, Greece, Tel.: +30-2810-392382, Fax: +30-2810-392382, e-mail: jpstamatiou@yahoo.gr

an oncologically sufficient treatment modality even for low-grade malignant rectal lesions such as Tis and T1 cancers, provided that preoperative diagnosis confirms the absence of lymphatic dissemination.[3] This procedure offers major advantages over the formerly used low anterior resection and abdominoperineal resection, which are characterized by significantly higher morbidity and mortality.[3] Since the anal sphincter and the autonomous pelvic nerves are spared, functional outcome is also ameliorated.[1] Major postoperative complications such as bleeding (1.7-2.7%) and pelvic sepsis due to perforation (1-2.7%) are rare.[4] In this case report, an exceedingly rare TEM postoperative complication, the presence of intraperitoneal "free air" with associated extensive retroperitoneal and mesentery emphysema in the absence of peritoneal defect is presented.

CASE REPORT

A 70-year old patient was referred to our clinic due to rectal bleeding. His medical history included Chronic Obstructive Pulmonary Disease (COPD) and Coronary Artery Disease (CAD). His surgical history included open cholecystectomy via a Kocher incision, as well as an appendectomy with associated peritonitis due to a ruptured appendix via a lower midline incision. The patient underwent full colonoscopy. Several pedunculated polyps were discovered and thoroughly removed from the ascending, descending and sigmoid colon respectively, while a large 6 cm long sessile polyp was cited 4 cm from the anal verge. Since the latter polyp could not be removed endoscopically, partial biopsy was taken. It revealed a villous adenoma with high grade dysplasia. On magnetic resonance imaging of the pelvis, the lesion was shown to invade the muscularis propria, with no signs of mesorectal or nodal invasion (T2N0). Computed tomography of the abdomen and chest did not reveal systemic metastases. Although abdominoperineal resection was proposed as the gold standard operation for such a large lesion, the patient strongly refused to have a permanent stoma and it was decided that he would undergo the TEM-procedure.

Before the procedure, antibiotic prophylaxis (Cefuroxime 1500 mg and Metronidazole 500 mg both once i.v.) was administered. Since the tumor was visualized on the ventral side of the rectum as shown on preoperative rectoscopy, the patient was placed in the prone position. The extended TEM-tube (TEO 15 cm, Karl Storz, Germany) was inserted and a pneumorectum was applied by insufflation of CO_2 at 6 L/min with a pressure limit of 12mmHg using a Karl Storz insufflator. Using ultracision, the tumour was macroscopically thoroughly removed (Figure 1). No perforation of the rectum to the peritoneal cavity was observed, and the rectal wall defect was closed using interrupted sutures. Since the lesion, as well as the rectal wall defect was quite large, the procedure was exceedingly long (180 min). The patient stayed for 6 hours in the recovery room due to persisting hypercapnia, before subsequently being transferred to the clinic.

On the first postoperative day, the patient complained of gradually progressive, yet painless abdominal distension as well as dyspnoea. Except for mildly increased respiratory rate, no other vital sign abnormality was observed, while CBC revealed mild leukocytosis with left shift (WBC: 12.0

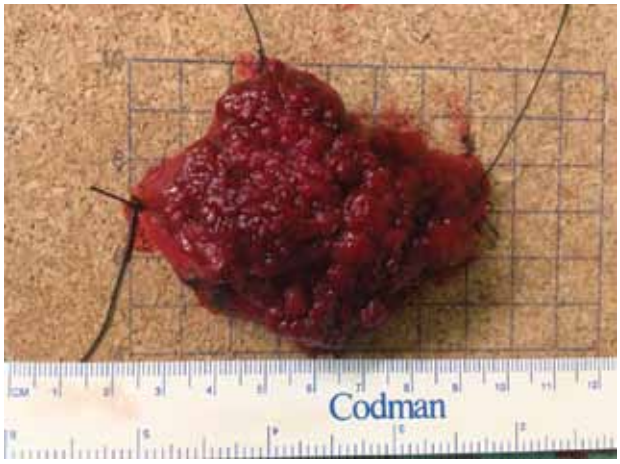

Figure 1. The surgical specimen.

x10^9/L, 78% neutrophils), that could potentially be attributed to the patient's postoperative condition. Hypercapnia ($PaCO_2$: 48mmHg) was noticed on blood gas analysis. The patient underwent erect chest and abdominal X-ray that revealed intraabdominal "free air", so rectal perforation in the abdominal cavity was suspected. The patient was emergently transferred to the operating theatre. An initial thought for diagnostic laparoscopy was soon aborted, due to the assumption that potential adhesions caused by the previous laparotomies might render the operation unfeasible, or at least, time consuming. A midline incision was made. No peritoneal defect was identified, while the abdominal cavity was free of inflammatory fluid or gastrointestinal content. Extensive emphysema of the retroperitoneum and the mesentery was observed instead (Figure 2 and 3). Abdominal fluid culture was taken; a drain was placed in Douglass space, and the abdomen was closed.

The patient was transferred to the recovery room and 5 hours later, to the clinic. He remained afebrile and made an uneventful recovery. The peritoneal fluid culture was sterile. He was discharged from the hospital on the 6th postoperative day, after he had received solid food and had had normal bowel movements. Histological examination of the lesion revealed an in situ carcinoma with clear resection margins.

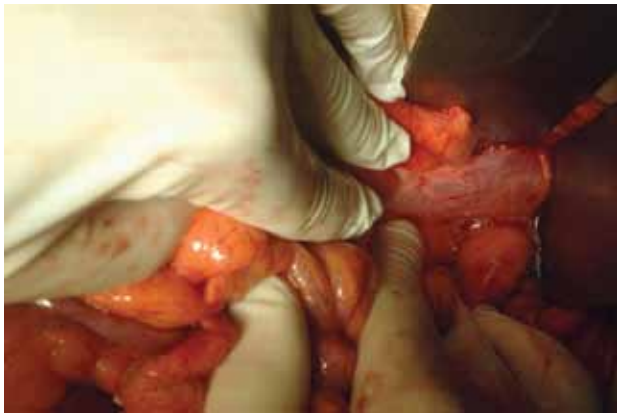

Figure 2. Emphysema of the mesenterium.

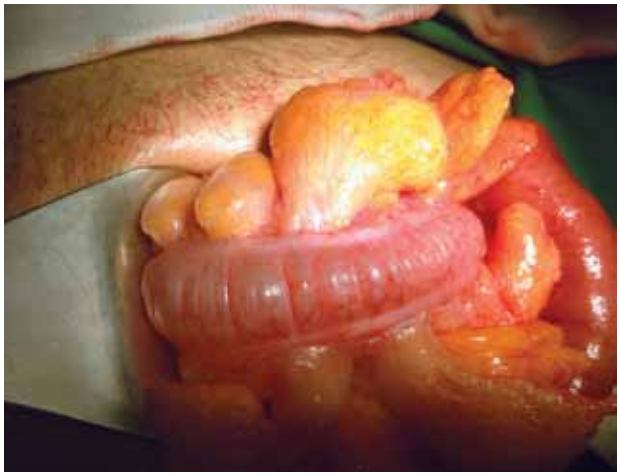

Figure 3. Emphysema of the appendices epiploicae of the large bowel.

DISCUSSION

Although the morbidity and mortality of the TEM procedure is extremely low compared to major rectal surgery,[5,6] its peritoneal entry rate may reach 9%.[7] Recent data suggest that peritoneal perforation during TEM does not necessarily mean conversion to laparotomy.[8] The data also suggest that TEM has no major or minor complications postoperatively,[6] no prolonged hospital stay,[6] and no long-term adverse oncological outcomes, provided that it is detected intraoperatively and closed primarily endoscopically.[6,9] Postoperative consideration of peritoneal perforation, as may be demonstrated by the presence of "free air" on erect chest or abdominal X-ray, necessitates close observation of vital signs, frequent abdominal physical examination, and serial blood tests as this is a potentially life threatening condition, often requiring emergent operation and formation of diverting colostomy.[1]

In the present case, although the presence of intraperitoneal "free air" on erect chest and abdominal X-rays suggested rectal perforation in the abdominal cavity, no peritoneal defect was identified on laparotomy. This strange condition was instead caused by the insufflation of CO_2 during the TEM operation.[1,10] More specifically,

since CO_2 is insufflated under pressure to create pneumorectum, and as a rectal defect including all its layers is created during TEM, CO_2 may, on rare occasions, escape to the retroperitoneum through the loose connective tissue instead of being eliminated by the mesorectal fat which usually seals the rectal wall defect.[1,10] The increased pressure of the accumulated CO_2 in the retroperitoneum, coupled with the decreased integrity of the retroperitoneal barrier, may lead to CO_2 diffusion into the peritoneal cavity.[1,10] This situation is extremely rare and only four such cases have been reported.[1,10,11] Exactly which factor triggered this extensive CO_2 escape and subsequent pneumoperitoneum in this patient over other TEM procedures remains, largely unknown. We hypothesize that the large rectal wall defect caused after resection of this apparently large lesion (6 cm), coupled with the extended operation time (180 min), may have played a role.

Due to the rarity of this entity, no specific diagnosis and treatment guidelines have been established, and so experience on the management of such patients is chiefly based on case reports.[1,10,11] Abdominal CT-scan with rectal contrast,[1,11] diagnostic laparoscopy,[10] and watchful waiting[10] have been suggested as means of diagnosis. At CT-scan, a significant amount of gas in the retroperitoneum and the mesorectum, a small amount of gas in the peritoneal cavity, as well as the absence of leakage of contrast from the rectal wound, are the main findings.[1] During laparoscopy, peritoneal bulging due to increased retroperitoneal gas pressure in the absence of a peritoneal defect, is seen.[10] Conservative treatment has been suggested,[1,10,11] provided that there is no suspicion of peritoneal entry during TEM,[10] the patient is in good condition and has no abdominal symptoms or signs of sepsis.[10] In our case, the patient's worsening dyspnoea and hypercapnia on blood gas analysis, in the context of his previous history of COPD which rendered him unstable and intubation imminent, deterred us from performing a CT-scan with contrast, and urged us to the operating theatre, where the patient would have sufficient monitoring, while definite diagnosis would be provided. Furthermore, laparoscopy, as noted above, was rejected, firstly due to the patient's previous laparotomies and secondly to our our assumption of resultant multiple adhaesions. Finally, life threatening hypercapnia in the early postoperative period has been associated with the TEM procedure, and is attributed to the insufflation of CO_2 into the rectum.[12] Thus, it is stressed that patients with arterial hypercapnia after TEM, as in our case, should undergo prolonged observation in the recovery room, until regular arterial blood CO_2 values are achieved.[12]

In conclusion, TEM has prevailed as a minimally invasive technique for the excision of certain rectal tumours. In this case report, we present a rare complication associated with this procedure, which should be effectively differentially diagnosed from the feared perforation to the peritoneal cavity. Such patients should undergo prolonged observation in the recovery room to prevent the consequences of severe hypercapnia.

REFERENCES

1. Simkens GA, Nienhuijs SW, Luyer MD, Ignace HJT de Hingh. Massive surgical emphysema following Transanal endoscopic microsurgery. *World J Gastrointest Surg* 2014; 6: 160-163.
2. Buess G, Hutterer F, Theiss J, Bobel M, Isselhard W, Pichlmaier H. Das System für die transanale endoskopische Rectumoperation. *Chirurg* 1984; 55: 677-680.
3. Leonard D, Remue C, Kartheuser A. The transanal microsurgery procedure: standards and extended indications. *Dig Dis* 2012; doi:10.1159/000342033.
4. Bignell MB, Ramwell A, Evans JR, Dastur N, Simson JM. Complications of transanal endoscopic microsurgery (TEMS): a prospective audit. *Colorectal Dis* 2010; doi:10.1111/j.1463-1318.2009.02071.x
5. Demartines N, Von Flue MO, Harder FH. Transanal endoscopic microsurgical excision of rectal tumors: indications and results. *World J Surg* 2001; 25: 870-875.
6. Gavagan JA, Whiteford MH, Swanstrom LL. Full-thickness intraperitoneal excision by transanal en-

doscopic microsurgery does not increase short-term complications. *Am J Surg* 2004; 187: 630-634.
7. Kunitake H, Abbas MA. Transanal endoscopic microsurgery for rectal tumors: a review. *Perm J* 2012; 16: 45-50.
8. Ganai S, Kanumuri P, Rao RS, Alexander AI. Local recurrence after transanal endoscopic microsurgery for rectal polyps and early cancers. *Ann Surg Oncol* 2006; 13: 547-556.
9. Baatrup G, Borschitz T, Cunningham C, Qvist N. Perforation into the peritoneal cavity during transanal endoscopic microsurgery for rectal cancer is not associated with major complications or oncological compromise. *Surg Endosc* 2009; 23: 2680-2683.
10. Franken RJ, Moes DE, Acherman YI, Derksen EJ. Free intra-abdominal air without peritoneal perforation after TEM: a report of two cases. *Case Rep Surg* 2012; doi:10.1155/2012/185429.
11. Cantos M, Bruna M, Garcia-Coret MJ, Villalba FL, Roig JV. Pneumomediastinum and subcutaneous emphysema like strange complications after transanal endoscopic microsurgery. *Rev Esp Enform Dig* 2009; 101: 445-446.
12. Kerr K, Mills GH. Intra-operative and post-operative hypercapnia leading to delayed respiratory failure associated with transanal endoscopic microsurgery under general anaesthesia. *Br J Anaesth* 2001; 86: 586-589.

GUIDELINES FOR AUTHORS

Hellenic Surgical Oncology is the official journal of the Hellenic Society of Surgical Oncology and publishes manuscripts related to all aspects of surgical oncology. The following types of manuscripts are published: editorials, review articles, original articles concerning clinical, experimental and/or research studies, case reports, discussions of controversial issues, reports of seminars, symposia, round table discussions and lectures, book reviews and letters to the Editor.

MANUSCRIPT SUBMISSION

The manuscript can either be emailed to **eis-iatriki@otenet.gr** or sent by post on a CD to the **Hellenic Society of Surgical Oncology, 76 Sevastopouleos Street, GR-115 26 Athens, Greece**.

Submission of a manuscript implies that the work described has not been previously published, that it is not under consideration for publication elsewhere and that the last version of the manuscript has been approved by all co-authors. When necessary, the manuscript should also be approved by the responsible authorities – tacitly or explicitly – at the institute where the work was carried out. The submission should be accompanied by a cover letter on behalf of all authors signed by the corresponding author, in which the above conditions are noted. The publisher will not be held legally responsible for any claims for compensation.

PERMISSION

Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

REVIEW OF MANUSCRIPTS

All manuscripts which meet the Journal's aims are reviewed. After the reviewers have sent their comments, the editing committee decides whether the manuscript is accepted, rejected or may be resubmitted after minor or major revisions as suggested by the reviewers. When the resubmitted manuscript is sufficiently improved, the manuscript may yet be accepted. Following approval, a manuscript proof is forwarded to the corresponding author. The purpose of the proof is to check for typesetting or conversion errors and the completeness and accuracy of the text, tables and figures. Substantial changes in content, e.g., new results, corrected values, title and authorship, are not allowed without the approval of the Editor. After checking, the proof with the final authors' comments has to be returned to the Editor for publication. Once papers are approved, the publisher claims exclusive publishing rights.

MANUSCRIPT PREPARATION

The manuscript should be written in proper English. The text should be submitted in an Ms Word file and written with double line spacing and a normal, plain font (i.e. 12-point Times Roman or 11-point Arial). The pages should be numbered consecutively. Field functions should not be used. For indents, use tab stops or other commands, but not the space bar. To create tables for the manuscript use the table function, not spreadsheets.

The submitted manuscript should include on separate pages: the title page, the abstract, the main text, references, tables and legends of figures.

Title page

The title page should include a concise and informative title in capital letters, the names of all authors (first letter of their first name(s) followed by their surname), the affiliations of the authors and the name of the corresponding author with his or her full address, telephone and fax numbers, and e-mail address. In case of case reports, 'Report of a Case' or 'Report of two (or three) Cases' should accompany the title as subtitle.

Abstract

The next page should include an abstract of 250 words maximum. The abstract of original articles should be structured with the following subheadings: Aim or Background, Material and Methods, Results, and Conclusion(s). The abstracts of case reports, review articles, discussions of controversial issues and reports of seminars, symposia, round table discussions and lectures do not need to be structured Editorials, book reviews and letters to the editors do not need an any abstract. The abstract should not contain any undefined abbreviations or unspecified references. Please provide 3 to 10 key words on this page which can be used for indexing purposes.

Main text

The main text of the *original articles* should be divided into the following sections: Introduction, Material and Methods, Results, Discussion (including conclusion(s)). The text of the manuscript together with title, abstract, references, tables and figures should generally not exceed 15 (double-spaced) typed pages.

Case reports should not exceed 10 (double-spaced) typed pages, with no more than 6 figures/tables. The text should be divided into: Introduction, Case Report and Discussion.

Review articles should be well structured and not consist only of a report of literature data that are available, but also of a critical discussion of these data and conclusions. Review articles should not exceed 20 (double-spaced) typed pages, while *editorials*, *book reviews*, *letters to the editor* and other reports should be concise.

Abbreviations should be defined as first mentioned and used consistently afterwards. Generic names of drugs and pesticides are preferred; if trade names are used, the generic names should be given at first mention.

Acknowledgments
Acknowledgments of people, grants, funds, etc. should be placed in a separate section before the reference list. The names of funding organizations should be written in full.

Conflict of interest
Authors must indicate whether or not they have a financial relationship with the organization that sponsored the research. This note should be added in a separate section before the reference list. If no conflict exists, authors should state: 'The authors declare that they have no conflict of interest'. The authors should have full control of all primary data and agree to allow the journal to review their data if requested.

References
Reference citations in the text should be identified by numbers in superscript at the end of the sentence or where the reference is explicitly mentioned. For example: 'Surgical oncology is considered a distinct discipline.[1,3-6]'; 'In a recent randomized trial,[2] the value of sentinel node biopsy …'; 'Johnson et al.[7] reported on a …'. The references should be numbered in order of appearance.
The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. The entries in the list should be numbered consecutively.
The reference of journal articles should include author(s), title and journal name, volume and pages. When the number of authors exceeds six, the first three should be mentioned followed by, "et al". Always use the standard abbreviation of the name of a journal according to the ISSN List of Title Word Abbreviations, **see http://www.issn.org/2-22661-LTWAonline.php.** Please see the examples below for journal articles and other types of references:

Journal article:
Paradisi A, Abeni D, Rusciani A, et al. Dermatofibrosarcoma protuberans: wide local excision vs. Mohs micrographic surgery. *Cancer Treat Rev* 2008; 34: 728-736.

Book chapter:
Miettinen MM, Mandahl N. Spindle cell lipoma/pleomorphic lipoma. In: WHO classification of tumors. Pathology and genetics of tumours of soft tissue and bone. Fletcher CDM, Unni K, Mertens F (eds). IARC Press, Lyon 2002; pages 31-32.

Online document:
Patel H, Smith KA. Use of spirit-based solutions during surgical procedures and safety guidelines. http://www.ma.gov.uk/Publications/CON0854. Accessed April 14, 2014.

Tables
Tables should be numbered using Arabic numerals and always be cited in the text in consecutive numerical order. Each table should have a concise title. Identify any previously published material by providing the original source in the form of a reference in superscript at the end of the table caption. Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and noted beneath the body of the table.

Figures
All figures are to be numbered using Arabic numerals. Figures should always be cited in the text in consecutive numerical order. Figure parts should be denoted in lower-case letters (a, b, c, etc.). The legends of the figures should be written on a separate page and be concise and descriptive.
Please supply all figures electronically. Indicate which graphics programme was used to create the artwork. Name your figure files with 'Fig' and the figure number, e.g., Fig1.jpeg. The figures should have adequate resolution. Black and white figures are published free of charge, but authors are requested to contribute to the additional costs for publishing colour art. When a person is clearly recognisable in a photograph, characteristics should be hidden (for example, eyes should be blocked) or written permission from this person for the publication of the unretouched photograph should be provided by the authors. When a figure has already been used in another publication, written permission for use from the copyright holder is required.

ETHICAL STANDARDS
Manuscripts of experimental studies submitted for publication must contain a declaration that the experiments comply with the current laws of the country in which they were performed. Please include this note in a separate section before the reference list.
Manuscripts of interventional studies submitted for publication must contain a statement to the effect that all human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. It should also be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted.
The Editor reserves the right to reject manuscripts that do not comply with the above-mentioned requirements. The Editor has the right to make changes in accordance with the guidelines set out in 'Guidelines for Authors'. The author will be held responsible for false statements or failure to fulfill the above-mentioned requirements.