QUARTERLY PUBLICATION OF THE HELLENIC SOCIETY OF SURGICAL ONCOLOGY


# Hellenic Surgical Oncology

September-December 2014 – VOLUME 5 – NUMBER 3

Hellenic
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
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***Professor Odysseas Zoras' election in the ESSO Board of Directors***

*It is a great honour for me to announce the election of our past President, Professor Odysseas Zoras, as a member of the Board of Directors of the European Society of Surgical Oncology (ESSO) during its biannual meeting in Liverpool last October.*

*This election reflects Odysseas Zoras' personal endeavors in the realm of Surgical Oncology worldwide and the recognition of his successful tenure as former President of our Society.*

*Odysseas Zoras, the only Professor of Surgical Oncology in Greece, is Director and Chairman of the Department of Surgical Oncology in the Medical School of Crete University Hospital.*

*The presence of our member on the Board of Directors of the ESSO both allows and enables our Society to be represented at the higher level of European administration in all the activities of its activity and acts as a beacon for the future advancement of Surgical Oncology in Greece.*

*The members of the Board of Directors of the Hellenic Society of Surgical Oncology and I congratulate Odysseas while stating that we are very proud of him and his activities.*

***John Spiliotis, MD. PhD***
*President of the Hellenic Society of Surgical Oncology*

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EDITORIAL

# Peritoneal carcinomatosis:
## The impact on the disease history of colorectal cancer

J.D. Spiliotis

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About 10% of patients with colorectal cancer develop peritoneal carcinomatosis during the course of their disease.[1] This condition is associated with significantly shorter overall survival when compared to non-peritoneal-carcinomatosis manifestations of metastatic colorectal cancer.[2] In the last twenty five years, prognosis of patients with metastatic colorectal cancer has improved dramatically with median OS increasing from <6 months to >20 months, due to the fact that development of new drugs has optimized systemic chemotherapy and due to the increased resection rates of liver and lung metastases.[3,4] Often, these results do not include peritoneal carcinomatosis patients because they are often classified as having "non measurable disease" by imaging techniques and these peritoneal carcinomatosis patients are often excluded from randomized systemic therapy trials. Although prevalence of isolated peritoneal carcinomatosis from colorectal cancer has been reported at 10 to 15%,[5,6] in a pooled analysis of North Central Treatment Group phase III trials N9741 and N9841 it was found in only 2.1% of cases.[2] A subset of patients presenting with bowel obstruction owing to peritoneal carcinomatosis have an even worse prognosis with a 17% one-year survival rate.[7]

The combination of systemic chemotherapy after complete cytoreductive surgery with concurrent hyperthermic intraperitoneal chemotherapy (HIPEC) has demonstrated a remarkable improvement in survival for highly selected patients with peritoneal carcinomatosis from colorectal cancer in a prospective randomized trial and several retrospective studies.[8-11] Many clinical trials concerning peritoneal carcinomatosis from colorectal cancer and HIPEC are in progress in the USA, France and Germany and are exploring the efficacy of HIPEC combined with systemic chemotherapy after aggressive cytoreductive surgery.[12] Another important aspect is to evaluate the role of second-look laparotomy in patients at high risk of presenting peritoneal carcinomatosis. Patients at high risk are those who have positive peritoneal lavage, mucinous T3 carcinoma or T4 adenocarcinoma, tumor rupture intraoperatively, invasion of adjacent structures and N2 status. In these patients, second-look operation one year after the initial surgical treatment and adjuvant systemic chemotherapy demonstrates 56% of "in situ" peritoneal seedings, which are asymptomatic.

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Second-look minimal cytoreduction and HIPEC offers a 5-year OS of 90% and a DFS of 44%.[12]

In conclusion, the management of peritoneal carcinomatosis from colorectal cancer has proven to be a challenge for both medical and surgical oncologists. In the past, the presence of diffuse implants in the peritoneal cavity denoted terminal stage disease. However, the current therapeutic approach is able to improve patient outcome. Cytoreductive surgery followed by HIPEC in combination with systemic chemotherapy has proven to be a very effective treatment modality and offers a ray of hope for cure.[13]

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HELLENIC SURGICAL ONCOLOGY 2014; 5(3): 108-110

REVIEW

# Pseudomyxoma peritonei for the general surgeon

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## ABSTRACT

**Pseudomyxoma Peritonei (PMP) is an uncommon entity that generally arises from a perforated appendiceal tumour. The gold standard treatment is cytoreductive surgery (CRS) combined with heated intraperitoneal chemotherapy (HIPEC). It's a disease that requires centralization and specialization for optimal results. The main recommendation in daily practice when faced with PMP as a preoperative or intraoperative diagnosis is not to proceed with resections, but rather, to refer the patient to a centre that can offer CRS plus HIPEC.**

**KEY WORDS:** pseudo myxoma peritonei, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy

## INTRODUCTION

PMP has an estimated incidence of two per million per year.[1] The typical appearance is diffuse mucous deposits in the abdominal cavity combined with mucinous peritoneal implants. A primary appendiceal tumour is the origin in the vast majority of cases. PMP is a clinical syndrome that has very diverse biological behaviour ranging from benign to very aggressive forms. There is a spectrum of disease ranging from an appendiceal adenoma combined with acellular mucin to frank adenocarcinoma with invasive peritoneal deposits. The long-term survival has been historically poor with reported a 5-year survival of 50%.[2] In the UK, two national centres are commissioned to treat this disease with treatment there being considered a highly specialized service. General surgeons will deal with one or two such cases during their career. Due to the diffuse nature of the disease, limited resections are not effective and render re-operations technically more demanding and dangerous. Conventional chemotherapy is not very effective. Adequate primary treatment is of major importance for the overall prognosis.

The natural history of PMP is one of progressive abdominal disease and intestinal obstruction not amenable to surgical interventions.[3] The conventional approach of repeated operations for symptomatic disease offers no hope of cure and results in a poor prognosis.[4]

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## PATHOPHYSIOLOGY

The commonest origin of PMP is the appendix.[5] Ovaries can be secondarily involved since they are the preferred site for deposits from appendiceal tumours. The increased incidence in women is most likely the result of quicker diagnosis since women with symptoms will have computer tomography scans for atypical low abdominal symptoms to exclude ovarian and uterine cancer. Ovaries, colon, stomach, pancreas and urachus can occasionally give also rise to PMP.[6]

Rupture of the appendix causes the escape of mucin from an appendiceal adenoma to the peritoneal cavity. Frequently, that event is not clinically noticed. The epithelial cells that have escaped continue to produce mucin with minimal and atypical symptoms. The distribution of PMP in the abdomen is characteristic.[6] The epithelial cells tend to concentrate around the liver, on the omentum, in the pelvis and the paracolic gutters primarily because of gravity and due to the normal flow of the peritoneal fluid. In later stages, the mucous is spread through the entire abdomen and causes intestinal obstruction and death. Due to the slow progress of the disease, many patients can live with the disease for many years. Initially small bowel loops are spared because of their mobility, but affected later in the course of the disease when minimal traumatic lesions at surgery enables adherence of mucinous tumour deposits.

In general, PMP can be classified into low-grade and high-grade tumours. Low-grade tumours behave in a benign way and have better prognosis, while high-grade tumours behave like appendiceal adenocarcinomas and are very aggressive. A detailed pathological examination of the specimen is crucial since the grading of the tumour determines prognosis.

## DISEASE EXTENT

The severity of the disease may vary. One may treat a non-perforated appendiceal mucocele which necessitates radical resection of the appendix as the only therapy. A locally perforated tumour and limited PMP of the right iliac fossa is very common in which case a right colectomy, an omentectomy and stripping of the right parietal peritoneum followed by HIPEC compose the surgical treatment. Extensive PMP on all peritoneal surfaces and various solid organs require multiple resections and peritonectomies. Imaging is not accurate in staging the extent of the disease and diagnostic laparoscopy is used to evaluate the small bowel involvement which is a relative contraindication for CRS and HIPEC. Liver and pulmonary metastases are very rare. On the other hand, involvement of the hepatic capsule is frequent and liver capsulectomy is then indicated.

## TREATMENT AND PROGNOSIS

Traditional management of PMP is repeated debulking surgery based on whether a patient is symptomatic or not. Memorial Sloan Kettering experience with serial debulking and systemic chemotherapy showed 5-year survival of 21%.[4]

Sugarbaker introduced the CRS plus HIPEC approach for PMP. The concept is that extensive surgery (CRS) including major resections and removal of the peritoneal surfaces in the abdomen can achieve macroscopic removal of the tumour while HIPEC deals with microscopic disease. This approach entails a 4-10 hour operation plus HIPEC and is associated with significant morbidity and mortality. There is obviously a steep learning curve. This approach offers a chance of cure, especially for low-grade tumours.[8,9] Sugarbaker and Chang published a series of 385 patients.[9] Patients with low-grade tumours had a better 5-year survival than those with high-grade tumours (80% vs. 28%) and patients with complete CRS had a better 5-year survival than those with incomplete CRS (80 vs. 20%). If complete cytoreduction cannot be achieved during surgery, most teams proceed to major debulking surgery because data show that it provides improved survival and better quality

of life when compared with palliative treatment.[10] CRS includes the removal of all disease and may include parietal peritonectomies, greater and lesser omentectomy, splenectomy, cholecystectomy, right/total colectomy, partial/total gastrectomy, low anterior resection and removal of the ovaries and uterus. Its major complication rate is significant. Therefore, this kind of operation needs to be performed at highly specialized units in order to achieve good results and acceptable morbidity. Selection of patients is crucial and, in general, frail patients with multiple co-morbidities are not ideal candidates for CRS and HIPEC.

Adjuvant chemotherapy is not beneficial for low-grade PMP. High-grade tumours are often given systemic chemotherapy but the results are inconclusive. Patients with low-grade tumours have excellent prognosis after CRS and HIPEC.

The most important prognostic factor for PMP is the completeness of cytoreduction.[8-10] CCR-0 indicates no visible residual disease, CCR-1 means residual disease of <2.5mm. CCR-2 stands for residual disease >2.5mm and <2.5cm while CCR-3 means that the residual nodules are >2.5cm in diameter. CCR-0 and CCR-1 resections are regarded as complete cytoreduction. Elevated tumour markers (CEA, CA 19-9 and CA-125) predict an increased risk of recurrence and reduced survival after complete CRS.[11] This may reflect cell biology in low grade tumours and is an independent prognostic feature. Further analysis may help to select patients for post-operative chemotherapy, second look procedures or stratification of follow up.

Centres that offer CRS and HIPEC must be accredited and audited. Due to the cost of the treatment and the possible complications, optimal surgery and management must be assured for the treatment to be effective.

## CONCLUSIONS

PMP is uncommon. CRS plus HIPEC is the treatment modality with the best results. If complete cytoreduction is achieved, excellent results ensue. As most general surgeons have limited knowledge of the management of this disease, the recommendation is to refer the patient to centres with resources and experience. In the cases where PMP is found intraoperatively, resections should not be performed and only biopsies should be taken.

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HELLENIC SURGICAL ONCOLOGY 2014; 5(3): 111-126

REVIEW

# Surgery for liver metastases

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**ABSTRACT**

**The liver is the most common site of metastatic disease from a variety of tumor types with colorectal cancer having the first place followed by neuroendocrine tumours (NETs) and then by non-colorectal, non-neuroendocrine tumours (NCNN). In recent years the approach of patients with liver metastases has changed. Surgery of liver metastases is now an established technique and the only one up to now capable to provide a cure, under certain circumstances and through careful selection of the patients. With the progress of imaging methods, surgery techniques and new chemotherapy treatments, more and more patients are candidates for curative surgical resection. In this study the surgical approach of the patients with liver metastases from colorectal cancer, NETs and NCNN tumours is presented.**

**KEY WORDS:** liver metastases, surgery, colorectal cancer, neuroendocrine tumours

## INTRODUCTION

Liver metastases are tumours that have spread to the liver from other areas of the body. As many as 50% of the patients with a primary malignancy will eventually develop metastases in the liver, a percentage greater than for any other organ, including the lung. Although primary tumours that drain principally into the portal circulation are more likely than others to develop hepatic metastases, many tumours arising in other sites, such as the breast and lung, also commonly develop hepatic metastases. Although the liver represents a common site of spread from many of these solid tumours, isolated hepatic metastases most commonly occur from colorectal cancer and, less frequently, from neuroendocrine tumours, gastrointestinal sarcoma, ocular melanoma, and others. For most other solid malignancies, the pattern of metastatic disease is most often that of generalized dissemination. Surgery for metastatic liver tumours has typically been the preferred therapy with the highest chance for long-term survival. During the past several decades there have been refinements not only in operative technique, but also in patient selection and perioperative care. These advances have led to the lowering of the mortality associated with liver resection. In turn, the scope of liver resection continues to expand, and, not infrequently, patients will have concurrent procedures combined with a liver resection. Patients with metastatic colorectal cancer represent the majority in whom resection may be indicated, but other tumour types are also appropriately resected in some cases. The purpose

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of this article is to review the data supporting resection in different tumour types and the surgical approaches, alone and in combination with other interventions, for the management secondary malignancies of the liver.

## DIAGNOSTIC APPROACH

The diagnostic process starts with a detailed medical history and a thorough physical examination. However, metastatic liver disease is usually diagnosed presymptomatically, through imaging. At the onset, virtually no evident symptoms or signs are present,[1] high temperature of unknown origin or unexplained episodes of thromboembolism may occur, but they are attributed to metastases only much later, when the disease has evolved. Large liver tumours may induce right upper quadrant or generalised abdominal pain. Additionally, weight loss and metabolic disturbances may develop. As the disease progresses, ascites, jaundice, portal hypertension, encephalopathy augur a bad prognosis.[1]

Laboratory tests like tumour markers as carcino-embryonic antigen (CEA) and biochemical markers for liver function evaluation are routinely used and support the diagnosis, though without great accuracy.

Only contemporary imaging modalities may establish an early reliable diagnosis.[2,3] Spiral computerised tomography (CT) show high accuracy in the detection and characterisation of liver lesions with sensitivity to 70%-90%.[4-6] Liver metastases can be distinguished as hypodense lesions in the portal phase. However, a CT scan cannot detect subcentimeter lesions.[4] Magnetic resonance imaging (MRI) is more useful than CT in detecting small metastatic lesions in a fatty liver, and in defining the relationship of the lesions to the hepatic vasculature and the biliary tree (MR cholangiopancreatography).[7] However, it has a sensitivity of 70% to 80% and it does not offer any significant advantage over a CT scan.[4] CT angiography and MRI angiography have gradually replaced the more invasive direct hepatic angiography and have a sensitivity of close to 90% in identifying hepatic lesions.[8,9] The contemporary imaging modalities are the considered methods of choice in deciding surgical resectability or the determination of an adjuvant therapy.[3] Imaging is improved by contrast agents, such as iodine for CT and gadolinium or superparamagnetic iron oxide for MRI.[10] CT or MRI may be chosen according to the local infrastructure of each centre (costs, availability and expertise) and the special characteristics of each examination. CT is a radioactive procedure and the use of iodine may provoke renal insufficiency or allergy; also, it is only 45% to 53% accurate in the detection of metachronous tumours, due to distorted liver anatomy after a surgical resection.[3,12] MRI on the other hand demands higher functional cost, longer time and prolonged breath holding by the patient.[3,10,13,14]

Ultrasonography (U/S) is not recommended in the primary diagnosis, due to its low accuracy.[3,14] However, it is often used in the detection of metachronous tumours as an initial imaging modality, because it is non invasive, inexpensive and widely available.[10]

FDG-PET is probably the most important imaging innovation, in the diagnosis of liver tumours. FDG (18F-flourodeoxyglucose) is a glucose analogue, which cannot undergo glycolysis and as colorectal metastases usually contain glucose in high concentration, this compound is used to localize them through positron emission tomography (PET).[2,10] FDG-PET can detect primary or recurrent, malignant or benign lesions, throughout the body, with high contrast resolution. Unfortunately, this method is unable to locate the tumours precisely.[2,11] Sensitivity has been shown to increase from 75% to 89% when CT and FDG-PET are combined, and is considered the gold standard.[16] PET/CT aims to improve PET's poor anatomical reference, with CT's high spatial resolution. It uses two scans located side by side, in order to compare the provided images. Integration of these images with expensive, specialised software makes the

procedure even more effective. Though, certain preconditions need to be fulfilled: identical patient positioning during PET and CT, difficult to follow breathing instructions, limited time gap between the two combined methods, great experience, and deep knowledge of a complicated software.[12] Hybrid hardware PET/CT fuses PET with CT in order to facilitate clinical practice, but the results are still premature. In the future, other new imaging modalities will appear, such as PET/MRI.[12] Italian and U.S.A. researchers found that PET/MRI outperformed PET/CT for swollen lymph nodes (lymphadenopathy) and tumours in regions that were difficult to assess with PET/CT, such as the kidneys, and achieved greater sensitivity with bony and hepatic metastases. PET-MRI is currently only available in highly specialized hospitals.

During the last two decades, laparoscopy (with or without laparoscopic U/S) has emerged as a new diagnostic modality for patients with liver malignancies. When laparoscopy is employed, unnecessary laparotomy can be avoided in 78% of patients with unresectable disease.[17] In these cases, laparoscopy can decrease the morbidity of surgery, and shorten the delay to systemic therapy.[18] Laparoscopy is indicated in cases in which the results of imaging studies are suspicious, but not diagnostic for extrahepatic disease, such as enlarged lymph nodes and peritoneal dissemination.

Intraoperative ultrasonography (IOUS), performed at laparotomy, has been an important tool for assessing resectability, and it remains in wide use. The sensitivity of open IOUS for detecting metastases is 96%, compared to 91% for CT angiography. Moreover, IOUS may alter management in 10% to 48% of cases.[19,20] IOUS can detect small intraparenchymatous lesions and in some cases, it causes the surgeon to change the planned resection because new lesions are identified or because unanticipated vascular involvement is detected. Open U/S, like laparoscopic U/S, continues to be used routinely, but it is likely that the yield will continue to decrease as better imaging becomes widely available.

Finally, biopsies should not be performed, because of the high risk of developing needle tract metastases.[10] Studies, which evaluated fine needle aspiration (FNA) for detection of various liver lesions, recorded 0.4% to 5.1% incidence of needle tract metastases.[15]

## COLORECTAL LIVER METASTASES

### Epidemiology and Natural History

Colorectal cancer (CRC) is the third most common cancer in the world and is increasing in incidence.[21] More than 50% of patients with CRC will develop liver metastases during their lifespan.[22,23] A quarter of patients with primary CRC are found to have synchronous hepatic secondaries.[24] Almost half of patients undergoing resection for primary CRC eventually develop metachronous liver secondaries. Historically the development of hepatic metastases had a poor prognosis with a median survival of approximately 5 months.[25,26] Newer chemotherapy agents have improved the median survival to over 20 months.[27] However, long-term survival after systemic therapy alone is uncommon, and surgical resection is the only therapeutic modality that offers the potential for long-term cure, with 5-year survival rates of up to 58%.[28,29] Historically, only 5%-10% of patients with colorectal liver metastases (CRLM) were resectable. Currently with the advances in diagnostic methods and new therapies, resectability rates have increased to 20%-25%.[30]

Even when hepatic resection is performed with curative intent,[31] 60% to 70% of patients will develop local or distant recurrence.[32] Recurrence occurs equally at intrahepatic and extrahepatic sites; 80% of all recurrences occur within two years. The median survival of patients with recurrent disease is 8 to 10 months without any treatment.[33] Repeat resection is feasible in 10% to 15% of these cases and may achieve a five-year overall survival rate of 15% to 40% in selected patients. Cure is considered after the achievement of 10-year disease-free survival.[34]

Hepatic resection for CRLM has developed over the past three decades. Appropriate patient selection and improvements in perioperative care have resulted in low morbidity and mortality rates, meaning that this is the therapy of choice in suitable patients.[35,36]

The indications for resectional surgery have evolved over time, and whilst the presence of multiple bilobar metastases was at one point a contraindication to surgery, this is no longer the case. Strategies for identifying those patients most likely to benefit from resection continue to evolve.[37,38] The current criteria for surgery revolve around the ability to achieve an R0 resection whilst leaving a sufficient residual volume of liver.[39,40] Many factors contribute to a successful outcome, and these include: accurate preoperative staging, neoadjuvant and adjuvant chemotherapy, operative planning, the use of combination treatments, such as preoperative portal vein embolization, and the two-stage resection approach when appropriate.[41,42]

### Operative morbidity and patient selection

Operative mortality for liver resections performed for metastatic colorectal cancer has decreased substantially over the past 3 decades to <5% in most series and is approximately 1% in high volume centres.[43-45] Reported major complication rates are greater than 20% in most series and are therefore an important issue.[46,47] Patient selection plays a critical role in minimizing mortality and morbidity following hepatic resection. Pre-existing comorbidities contribute substantially to surgical morbidity and mortality. Therefore, one goal of the preoperative evaluation should be to exclude patients with prohibitive operative risks and to identify patients with manageable conditions that can be medically optimized before operation.

Advanced age is not a contraindication to hepatic resection which is now routinely performed in elderly patients with acceptable morbidity and mortality.[48,49] Some centres have demonstrated that the American Society of Anesthesiology (ASA) and Acute Physiology and Chronic Health Evaluation (APACHE) scores can be useful in predicting complications.[50,51] Although such surrogates of physiological conditions can help predict complications in this patient population, they fail to provide guidelines for managing co-morbid conditions in the perioperative setting. Performance status and frailty are very important predictors of perioperative outcome and are routinely evaluated at the preoperative visit.[52,53] Patients are evaluated for their co-morbid conditions by appropriate sub-specialty services and risk stratified. Patients must be fit for a major laparotomy, the metabolic consequences of a hepatic resection and the attendant substantial physical recovery.

All patients being considered for a hepatic resection should be assessed for preoperative liver dysfunction. Although most patients with colorectal cancer do not have underlying chronic liver disease, exposure to chronic chemotherapy can result in hepatic steatosis, steatohepatitis, sinusoidal obstruction syndrome and even portal hypertension.[54,55] Steatosis and steatohepatitis also frequently occur in the general population but are likely exacerbated with chemotherapy treatment. Patients with significant portal hypertension have a very high risk of mortality associated with hepatic resection and are generally not considered candidates.[56] The most common system of evaluation of liver function among patients with underlying cirrhosis is the Child-Pugh classification. The Child-Pugh score includes two clinical factors (ascites and encephalopathy) and three laboratory parameters (bilirubin level, albumin level, and prothrombin time). Surgical resection is most often considered in Child-Pugh A and very well-selected Child-Pugh B patients. Another useful preoperative tool to assess the risk of postoperative liver failure is the Model for End-stage Liver Disease (MELD) (table 1). Several studies have shown that a MELD score more than 10 is associated with a higher risk of postoperative liver decompensation and mortality in patients with cirrhosis.[57] As such, several investigators have advocated the use of the "native" MELD as a tool for allowing a better selection of candidates for major liver resection. Another tool to evaluate hepatic metabolic function is the indocyanine

green (ICG) retention rate galactose elimination and aminopyrine clearance. This method, however, is not widely used in Western countries. In particular, patients with a normal liver should have an anticipated future liver remnant (FLR) at least 20%, whereas patients with a steatotic or cirrhotic liver should have an anticipated FLR at least 30%. Determination of the FLR can be achieved with the use of preoperative contrast-enhanced CT or MRI volumetry.

### Current criteria of hepatic resection

During the past two decades the five-year survival rates for hepatic colorectal metastases patients have almost doubled, from 30% to 60%.[33] The introduction of new chemotherapeutic agents and the shift in the criteria of surgical resection were the main factors in this progress.[58] Previous absolute or relative contraindications to resection included the presence of extrahepatic disease,[37] involvement of hepatic pedicle lymph nodes,[59] and an inadequate resection margin of <1 cm.[60] All above contraindications for hepatic resection have been challenged and have already lost their importance in patient selection for hepatectomy.[61,62]

The current criteria focus on what should be left after hepatic resection. Nowadays, the definition of resectability includes a complete resection with tumour-free surgical margins (R0 resection), sparing at least two liver segments having an independent inflow, outflow, and biliary drainage. The amount of the liver remnant after resection should not be less than 20% and 30% of the total liver volume in normal and cirrhotic patients, respectively. This can be accurately predicted by CT or MRI during preoperative evaluation.

### Prognostic factors

The microscopic status of the resected margin is the most important prognostic factor for overall survival, and incomplete tumour removal is often damaging to the overall long-term outcome. The presence of a positive margin increases recurrence rates, and reduces overall and disease-free survival.[63] The effect on prognosis with extrahepatic disease has also been shown to be detrimental, however some research has proven the opposite.[64]

A number of additional factors have been identified in the literature with regards to prognosis after liver resection. The most common factors include: liver portal lymph node metastasis, number of metastases, a positive resection margin, the presence or absence of extrahepatic metastasis, and synchronicity/metachronicity. Other primary tumour factors consist of the degree of differentiation, depth of wall invasion and positive lymph node metastasis. Metastatic lesion factors, however, include >4 individual tumours, degree of differentiation (poorly differentiated), and maximum tumour diameter, one surgical factor is a resection margin of <10 mm and background factors include high carcinoembryonic antigen (CEA) before hepatectomy and disease-free duration of <1 year.[64,65]

Another important factor effecting prognosis for a patient undergoing liver resection is the response to systemic chemotherapy (CTX).[66] Many studies have shown that if tumour progression continued whilst receiving CTX (oxaliplatin or irinotecan-based) this was independently associated with decreased survival rate.[67]

Other prognostic factors that remain a subject of debate are the spread to lymph nodes by the original CRC and the maximum size of metastases.[64] Another factor investigated was the interval between the CRC operation and detection of CRLM, while some studies support this,[65,68] others contradict it as a predictive factor.[69,70] The difference between synchronously and metachronously presenting metastases has also been investigated and the majority of studies have shown that it lacks prognostic value.[64] Studies have also failed to show bilobar spread as a prognostic factor.[64,68,70]

### Management of colorectal liver metastasis with synchronous peritoneal carcinomatosis

Both separate sites of metastasis have been curatively treated by surgery, and cases have been

reported of patients with peritoneal metastases (PM) of colorectal cancer that have been treated with a combination of resection, including that of liver metastases and hyperthermic intraperitoneal chemotherapy (HIPEC). This has proven to be feasible.[71]

Despite the fact that the presence of CRLM is formally a contraindication for cytoreductive surgery and HIPEC, there is a selected group of patients presenting with a combination of CRLM and PM that may be curatively treated by an aggressive surgical approach.[72,73]

In 2008, a consensus was agreed upon, stating that concomitant liver metastases are only to be resected when confined to three or less well-resectable lesions.[74,75] In addition, eligible patients should have a good performance status and low co-morbidity.[76]

### Synchronous colorectal liver metastases: simultaneous versus staged resection

Synchronous hepatic metastases occur in about 20%-30% of newly diagnosed colorectal cancers, and they present a challenging problem in the management of these patients.[77] Consensus has not been reached as to the timing of surgical resection of the hepatic secondaries and the primary colorectal tumour. In resectable patients the decision is whether colon and hepatic resections should occur as a single combined procedure or staged. There are three options including staged resection with 'colon first', staged with 'liver first', or simultaneous resection.

Traditionally, these patients were managed by a second laparotomy 2 to 3 months after the resection of the primary tumour.[78] A delay in resection of synchronous secondaries is justified by the need to recover from the primary resection, or if the patients have comorbidities that require optimization of medical condition. However, with advances in perioperative care and the continuous improvements regarding the postoperative morbidity and mortality rates after liver resection, most researchers today support simultaneous resection.[79,80] A recent multicenter international analysis compared simultaneous resections to staged (colon first and liver first) in over 1,000 patients and found no significant difference in morbidity, mortality or long-term oncologic outcomes between any of the three sequences.[81] In addition, a recent meta-analysis confirmed no difference in oncologic outcome between staged and simultaneous resection, and a shorter hospital length of stay and lower morbidity with simultaneous resection.[82] On the other hand, others stated that there was no difference in survival rates between patients undergoing synchronous and metachronous resections, and that secondary metastases tend not to occur after removal of the primary tumour.[83] They concluded that metachronous resection should be performed, and synchronous resection should only be recommended if there is a possibility that metastatic lesions may grow during the waiting period and become harder to resect. Some studies have shown an increase in mortality when the primary has been combined with major hepatectomy. According to a recent expert consensus the priority in staged resection may be given to 'colorectal first' or 'liver first' strategies based on concern for complications related to the primary tumour, such as obstruction, perforation, or bleeding, or the progression of marginally resectable CRLM during treatment of the primary.[84] The decision to do simultaneous resections is based on the overall complexity of both procedures and the patient's comorbidities.[84] The 'liver first' sequence is most suited to rectal cancers so that the liver metastases are not left untreated during the radiation portion of treatment to the rectum.[84]

Whichever order of procedures is used, R0 resections need to be obtained at both sites. If liver metastases are not resectable, resection of the primary tumour does not improve survival and should only be used in patients with symptoms that are not controlled with less invasive techniques.[85] However, no real indications or contraindications exist for simultaneous resection

of hepatic metastases, and it seems that the final decision depends on the surgeon's experience and the patient's physical status.

## How to increase resectability

No existing treatment other than surgery can result in long-term survival, but only 10–20% of patients with liver metastases fulfils standard selection criteria and is amenable to surgery. As a consequence, the trend is to be more aggressive and to increase the indications for surgical resection. Neoadjuvant chemotherapy, portal vein embolization and two-stage hepatectomy may render amenable to surgery patients that would have been refused some years ago.

### *Neoadjuvant chemotherapy*

The use of preoperative chemotherapy may exert a downsizing effect on the metastatic tumours, so one may perform surgery as soon as resectability is technically feasible. In patients with disease initially determined to be anatomically unresectable, modern preoperative chemotherapy allows complete resection in 12.5-32.5% of patients.[83,86] These regimens include FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and FOLFIRI (folinic acid, fluorouracil, and irinotecan) most commonly and more recently the use of the monoclonal antibodies bevacizumab or cetuximab in combination with chemotherapy to increase response rates.[87] In the attempt to enhance treatment results and to increase the proportion of patients exposed to all active agents, a combined administration of 5FU/LV, irinotecan and oxaliplatin (FOLFIRINOX) has been developed.[88,89] In a well designed study, FOLFIRINOX showed to be more effective than FOLFIRI and was associated with a higher secondary resection rate of liver metastases (36% vs. 12%). This regimen was particularly toxic and requires special precautions.[88] FOLFIRINOX is an interesting regimen particularly in neoadjuvant setting for the management of potentially resectable CRLM. The most important problem associated with neoadjuvant chemotherapy is the progression of metastases during neoadjuvant chemotherapy.[90]

Neo-adjuvant chemotherapy can also be used via hepatic arterial infusion (HAI) with high response rates.[89] Patients with metastatic lesions confined to the liver, without severe ascites or jaundice, are ideal candidates.[92] Preliminary data from several clinical trials with oxaliplatin or irinotecan via HAI have been promising.[93] However, HAI is rarely used outside specialized treatment centres, because of limited expertise, high cost of infusion pumps, and ongoing concerns regarding the considerable morbidity due to catheter-related complications, particularly sclerosing cholangitis.[94]

### *Portal vein embolization*

Although a tumour is technically resectable, resection can be contraindicated if the future remnant liver is too small to provide sufficient postoperative liver function. In such cases, preoperative selective portal vein embolization (PVE) has been proposed to induce ipsilateral atrophy and contralateral compensatory hypertrophy of the remnant liver, thus preventing postoperative liver failure.[95] PVE has been reported to result in a 7-27% increase in the FLR and the time for maximum regeneration ranges from three to nine weeks [101].[96-99] PVE can be performed under conscious sedation by interventional radiology under sonographic and fluoroscopic guidance.[96,97] Thrombosis, migration of the emboli to the contralateral hepatic lobe, haemobilia, haemoperitoneum, and transient liver insufficiency, are complications occurring in 10% of cases and can be easily managed.[100] There is a concern that tumours could have increased growth rates following PVE in both the embolized and non-embolized lobes. The hypothesis states that by increasing hepatic artery and portal blood flow there is an increase in local growth factors, leading to tumour growth [97,98].[101,102] Several studies have indeed demonstrated this in colorectal metastases.[101,103,104] The addition of chemotherapy between PVE and resection has shown success in slowing tumour progression, and improving long-term survival for PVE patients.[102]

### *Two-stage hepatectomy*

Two-stage hepatectomy can accomplish complete resection of disease that is initially unresectable, resulting in improved survival over comparative patients treated with chemotherapy only.[105] There are two different approaches. In first approach the highest possible number of metastatic tumours are resected first, and the remaining are resected in a second procedure after a period of liver regeneration.[106] In the second approach usually begins with 4-6 cycles of systemic chemotherapy. Repeat imaging is obtained and patients with response or stable disease undergo the first-stage resection. The first-stage resection usually involves resection of all metastases from the future FLR in the form of minor resections that avoid hilar dissection or mobilization of the contralateral liver.[107] Often PVE is necessary at this stage to increase FLR prior to the second-stage resection. Resecting all disease in the FLR prior to PVE also avoids the increased tumour growth rate seen following PVE.[101] After 4-6 weeks, typically with or without chemotherapy, repeat imaging is obtained to assess for liver regeneration and second-stage resection then follows.[84] Morbidity following the first procedure is 11-17% with negligible mortality.[105,108,109] It is important to minimize morbidity after this first stage to ensure the subsequent resection because there is no benefit of just the first stage for survival.[105] The second stage resection is completed in 76-87% of patients who undergo the first stage.[105,108,109] The R0 resection rate for the second stage procedure is 58-79%.[105,109] The 3-year overall survival ranges from 50% to 84% for patients completing both stages of resectio.[105,108,109] This survival is a reflection of both selection of favourable biology and complete resection of metastatic disease.[105]

## Ablation techniques

Ablation techniques aim to induce local destruction of the CRLM. At present, the exact role of ablative techniques in the treatment of CRLM is unclear, although there have been suggestions that its roles may include to reduce tumour size minimizing the extent of liver resection required, adjunctive therapy for patients either unfit for surgery or with unresectable disease. Ablative approaches can be subdivided into cryoablation, radiofrequency and microwave ablation.

### *Cryoablation*

Cryoablation was the first thermal ablative modality attempted to treat unresectable hepatic malignancies.[110] Cryoablation application appears to vary between institutions. In general, its primary use has been for the ablation of unresectable CRLM. Despite initial thoughts that cryoablation could be used in patients with resectable CRLM, high tumour recurrence following cryosurgery has tempered this enthusiasm. So far, previous research has demonstrated a modest 5-year survival of 26%, but also low mortality rates of less than 5% following cryotherapy for CRLM.[111] Cryoablation used in combination with surgery has also been shown to produce similar survival benefits to surgery alone in patients with initially unresectable CRLM.[112]

### *Radiofrequency ablation*

By far, the most extensively evaluated ablative approach is radiofrequency ablation (RFA). RFA is the most widely applied ablative modality due to ease and safety of application and inexpense of equipment.[113] This modality is applied by placing needles within and adjacent to CRLM through which alternating electrical current is delivered at radiofrequency range generating heat to desiccate the tumours.[114,115]

Although RFA is in widespread use across many institutions internationally, a paucity of randomized controlled trials up to now has prevented the development of a consistent approach to its use. Indeed, to date, there are no RCTs comparing surgical resection with RFA in resectable CRLM, a study that at present seems inconceivable and unethical considering established survival data from surgical resection. At present, most evidence from the retrospective studies available comparing RFA and resection has demonstrated the

inferiority of RFA compared to surgical resection with increased local recurrence rates (16%-60% vs. 0%-24%) and worse long-term survival.[115,116]

At present, RFA is being used to treat unresectable CRLM only, with no extrahepatic metastatic disease.[117] Tumours amenable to successful treatment with RFA have typically been solitary CRLM or a few which are not close to large hepatic vessels.[117] Tumour size in particular has been limited to 3-cm due to the circumferential rim of ablation currently delivered by ablation probes being approximately 4-cm in diameter, a limitation that may be addressed with advancement of the technology. Overlapping ablations can be used to treat larger tumours although this has been associated with less successful complete ablation.[118] The presence of large blood vessels limits RFA efficacy because their high blood flow acts a "heat sink", protecting adjacent cells from thermal ablation.[113]

RFA is delivered via open, laparoscopic or percutaneous approaches.[117] The application of ultrasound, CT and MRI are particularly important to guide the needle in the percutaneous approach while intraoperative ultrasound is an additional adjunct used to directly visualize the tumour in the operative approaches. It appears at present, that RFA via laparotomy is associated with the lowest recurrence rate followed by laparoscopy, and finally by percutaneous approach. The trade-off of using the least invasive percutaneous approach must be weighed up against poor tumour visualization increasing the potential for recurrence. The surgical approaches are typically applied at the time of primary or hepatic metastasis tumour resection.

In addition to the aforementioned advantages of RFA, it has a relatively lower morbidity profile of <10% independent of the approach used for delivery being surgical or percutaneous.[119] Amongst the complications that have been seen, thermal injury (bowel and biliary injury), mechanical (biliary and vessel injury) and septic (abscess and peritonitis) have been the most widely reported. A more infrequent presentation of post-ablative syndrome where patients suffer from self-limiting constitutional upset including malaise, febrile episodes, myalgia, nausea and vomiting has also been reported.[117]

### *Microwave ablation*

Microwave ablation (MWA) is a more recently developed technique used for CRLM. MWA is applied via a microwave probe delivered into the tumour via image-guided percutaneous, or ultrasound guided surgical approaches. Via these probes, microwave radiation between 900 MHz and 2.4 GHz is delivered that causes polarized water molecules within the tissue to oscillate generating friction that produces heat that destroys tissue by coagulative necrosis.[120]

As this modality is relatively new, the evidence of its efficacy is limited and has included too many different liver tumour types particularly hepatocellular carcinoma. The exact application of MWA for CRLM is therefore still unclear. Although reported local recurrence rates have been extremely variable ranging from 3% to 50%, encouraging evidence from the largest series reported rates as low as 3% and 6%.[121,122] Further research would therefore provide the evidence to define its role as an ablative therapy in CRLM management.

The purported advantages of MWA have been the more extensive nature of tissue destruction created by the heating mechanism generated by this technique. This mechanism also appears to be less prone to the "heat-sink" effect seen with RFA therapy.[123] The complication rates from MWA range from 6% to 30%, most often associated with cases where laparotomy and additional procedures had been performed.[114,121,122] There are at present concerns of potential inadvertent injury to surrounding organs due to the higher energy generated by this modality.

## Recurrence and repeat resection

Up to 55%-60% of patients will develop recurrent liver metastasis, the majority within the first 2 years.[124] Even when liver resection is performed with curative intent, 60%-70% of patients will

develop local, regional, or distant recurrence.[124] Multiple studies have shown that the results of repeated curative resection are comparable to the first resection in terms of overall survival,[125] and compared to the first resection, the only difference of the second and the third hepatectomy is that the surgical technique becomes more difficult.[63] The reported morbidity and mortality rates and long term survival rates of re-resection are similar to those reported for the original hepatectomy despite the greater technical difficulty of the procedure.[126] Long term survival appears to be similar to that for the initial hepatic resection.[126,127] However, patients with a low tumour load appear to be the best candidates and the presence of extrahepatic disease or incomplete tumour clearance is associated with a poorer outcome.[128] It seems appropriate to consider such lesions in the same way as the initial hepatic metastases and to offer re-resection or ablation to patients based on operative risk and likely survival.

## NEUROENDOCRINE TUMORS (NETS) AND LIVER METASTASES

Neuroendocrine tumors (NETs) constitute the second largest indication for surgical treatment of liver metastases, after colorectal cancer. NETs are slow growing heterogeneous neoplasms, which are generally viewed with a favourable prognosis. After the lymph nodes, the liver is the predominant site for NETs metastases. Synchronous liver metastases present in 75-80% of patients, which is a key adverse prognostic factor. When it is feasible, aggressive surgical management of both the primary tumour and the liver metastases improve overall survival rates extensively.[129,130] Numerous studies have confirmed complete hepatic resection for liver metastases has significantly improved long-term survival compared to other conservative treatments.[130-133] Aggressive surgical resection increases the 5-year survival of NETs with solitary liver metastasis to 100%, where disseminated metastatic NETs suffer a 51% 5-year survival rate after surgical resection.[134] Liver transplantation should be considered another surgical option when both surgical and medical treatment fails to eradicate disease.[135,136] Liver transplantation is a feasible option for young patients (<50 years old) with unresectable tumour, low ki-67 index and no extra-hepatic disease.[137,138]

## NON-COLORECTAL, NON-NEUROENDOCRINE LIVER METASTASES

The role of metastasectomy for colorectal and neuroendocrine liver metastases is well established. Significant palliation and survival have been reported after aggressive surgical resection. The indication for the surgical resection of liver secondaries from non-colorectal, non-neuroendocrine (NCNN) tumours is less well defined. The decision to proceed with liver resection in a patient with NCNN metastases must come after thorough evaluation. Selection of patients with favourable tumour biology is the key point in defining which patients will benefit most from liver resection. Primary tumour type is the most common prognostic factor described, and favourable survivals are generally reported for genitourinary, breast, and soft tissue sites. The disease-free interval between treatment of the primary tumour and development of liver metastases is viewed as a marker for tumour biology. The notion of a longer disease-free interval possibly being associated with less aggressive tumour biology is supported by studies demonstrating longer survival in patients with disease-free intervals more than 12 or 24 months. The third relevant prognostic factor is a complete resection with tumour-free surgical margins (R0 resection).Improvement in preoperative staging and progressive application of development of new multimodality treatments will be the key to improved survival in this disease.[139-142]

## CONCLUSIONS

Thirty years ago patients with liver metastases were regarded as non-operative cases and they had

no hope to be cured. Nowadays a big percentage of these cases can be dealt with through surgery and have encouraging results. With the progress of science, by using up-to-date imaging means, by discovering new chemotherapy treatments and with the introduction of new surgical equipment and techniques, more and more patients are candidates for therapeutic approach of liver metastases. Currently an operation is the key to treatment, this means that more trustful surgical techniques are being adopted and broaden the criteria in order to carry out surgery. Attention is needed for the selection of the patients through individuation so that the postoperative mortality does not surpass the natural selection. In the colorectal liver metastases there has been a big advance. It is not a lie though to say that what we know today about the metastatic disease of the liver from NCNN tumours is of the same level with what we knew about the colorectal thirty years ago. There is still a long way to go.

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HELLENIC SURGICAL ONCOLOGY 2014; 5(3): 127-133

ORIGINAL PAPER

# Basal cell carcinoma of the eyelids and reconstruction options

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## ABSTRACT

**Aim: Excision of skin cancer of the eyelids is always a demanding procedure where adequate margins and good aesthetic and functional outcome are expected while leaving very little space for reoperations. The aim of this study was to evaluate the experience of our department with reconstruction of the eyelids after excision of basal cell carcinoma. Material and methods: In a 10-year period, 52 patients with basal cell carcinoma of the eyelids underwent reconstructive surgery after excision of the tumour. Results: Various surgical reconstructive procedures were used. The choice of the reconstructive technique depended on the size, the site and the thickness of the defect. A pentagonal or wedge excision with or without tissue advancement, a Langebeck flap, an Esser rotation flap, a glabellar flap, a V to Y flap, a skin graft, a Fricke supraorbital musculocutaneous flap and a large transposition flap of the forehead (only in the case of a major surgical excision of both eyelids or after globe exenteration) were used. Conclusions: Traditional methods and reconstruction options of the eyelids can always yield good results after appropriate presurgical planning in order to obtain the maximum advantage from the local tissues of the periocular area.**

**KEY WORDS:** basal cell carcinoma, eyelid, reconstructive surgery

## INTRODUCTION

The most common site of a malignant lesion of the eyelid worldwide is the lower lid followed by the medial canthus, while the most common carcinoma of the lids is the basal cell carcinoma.[1] Skin cancer of the eyelids almost always necessitates ablative surgical procedures. Due to the complex anatomy of the eyelid, a reconstruction plan, assessing the skin, muscle, supporting structures and conjunctiva, should be used in order to restore the aesthetic and functional needs of the periocular area. In planning such reconstructive surgery, knowledge of the anatomy and function of the eyelids and their adjacent structures is most essential.

Eyelids are a complex structure of mobile soft tissue anterior to the globe. The upper eyelid is mainly responsible for the opening of the eye while the lower eyelid is slightly retracted only during the downward gaze.[2,3] The upper eyelid is retracted by the levator palpebrae superioris muscle which

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is inserted to the upper end of the superior tarsus and the superficial skin about 8 to 10 mm from the palpebral fissure creating a furrow, the superior sulcus. A mild contribution to the eyelid retraction is offered by the Muller's muscle which is a small muscle deep near the levator aponeurosis and is innervated by the sympathetic nervous system.[4]

Closure of the eyelid is achieved by the action of the orbicularis oculi muscle. This muscle is a circular muscle which can be divided topographically into three parts, named pretarsal, preseptal, and orbital. Soft closure of the eyelid is achieved by the action of the pretarsal and preseptal orbicularis only while forced closure of the eyelids is maintained by the retraction of the orbital division of the muscle.

The eyelid in cross-section (Figure 1) can be thought of as a bilamellar structure with an anterior and a posterior lamella separated by the orbital septum and the tarsal plate. The septum is formed by the confluence of the periosteum of the orbit and the periosteum of the facial bones beginning from the orbital rim and extending towards the superior and inferior tarsus. The anterior lamella is comprised of skin, subcutaneous tissue and the orbicularis oculi muscle and the posterior lamella is the palpebral conjunctiva.[3]

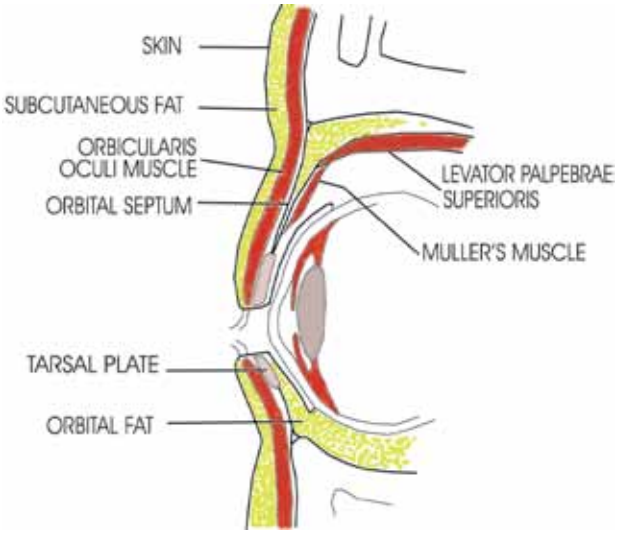


**Figure 1.** Anatomy of the eyelid and adjacent structures.

Along their lateral and medial margins, the upper and lower tarsus coincide with the lateral and medial canthal tendon respectively, which subsequently insert to the zygomatic bone laterally and the maxilla medially. At the free margin of the lids the cilia (eyelashes) are exhibited near the skin while deeper and nearer to the conjunctiva, the orifices of the Meibomian glands discard their sebaceous exudation.

The lacrimal gland is situated in the lacrimal fossa of the superolateral orbit and the upper lateral eyelid and excretes fluid which is analogous to that of the salivary glands. Tears reaching the medial aspect of the palpebral fissure are drained into the nasal cavity by a system of ducts beginning with the superior and inferior lacrimal punctus at the medial free margin of the lids.

In this manuscript, we evaluated the surgical procedures performed in our department during a 10-year period to reconstruct the soft tissue defect after excision of basal cell carcinoma of the eyelids.

## PATIENTS AND METHODS

From 1996 to 2005, 52 patients with basal cell carcinoma of the eyelids underwent various reconstructive procedure options to cover the soft tissue defects that were the result of excision of the tumour. Patients with malignancies of adjacent areas extending to the eyelids were not included. The age of the patients varied from 34 to 93 years of age (mean: 69 years). There were 26 male and 26 female patients. In 70% of the cases, the skin tumour was ulcerated, while in 19% of the cases the basal cell carcinoma was metatypical (intermediate type between basal and squamous cell carcinomas). The median defect diameter was 2.2 cm or 75% of the lid length. In two patients the lesion had spread to the eye globe making exenteration necessary. The distribution of the basal cell carcinoma according to the periocular areas was: upper lid in 7.7%, lower lid in 54.4%, medial canthus in 28.3% and lateral canthus in 9.6% of the cases.

## RESULTS

Various reconstructive surgical techniques were used according to the kind of defects. The pentagonal or wedge excision[5] with or without tissue advancement and direct closure had been used in 12 cases for partial thickness defects of the lid conjoined with lateral cantholysis where it was necessary for full thickness defects (Figures 2-4).

The use of a Langebeck flap[6,7] was always the method of choice for great full thickness defects of the lower lid, when a composite mucocartilaginous graft of the nasal septum would restore the deep lamella of the lid giving structural support. The Langebeck flap is a transposition cutaneous flap from the cheek area, used to restore the superficial lamella of the eyelid in 7 patients (Figures 5 and 6).

The Esser rotation flap[3,8] was used in 9 patients for larger defects utilizing the skin abundance of the cheek and is a classic method of reconstruction for the lower lid and the zygomatic area (Figures 7 and 8).

The glabellar flap[3,8] is a transposition advancement flap, which was suitable in restoring medial canthal defects with glabella skin in 5 cases (Figures 9 and 10). A V to Y flap is a sliding advancement flap that can adequately mobilize tissue from the

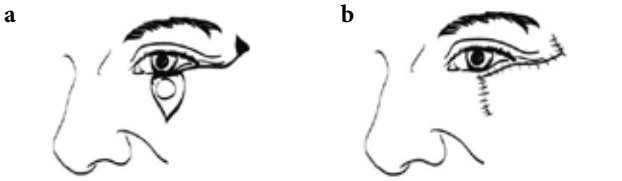


**Figure 2.** Schematic view of wedge excision of lower eyelid tumour (a) and direct closure of the defect with tissue advancement (b).

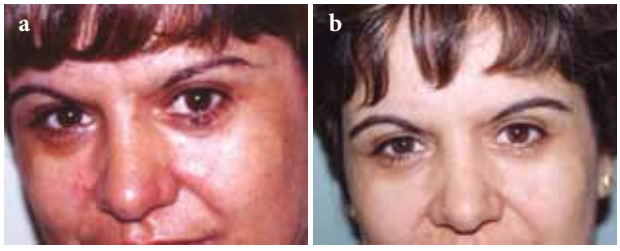


**Figure 3.** A patient with a basal cell carcinoma of the lower eyelid (a) two months after wedge excision of the tumour with direct closure of the defect with tissue advancement (b).

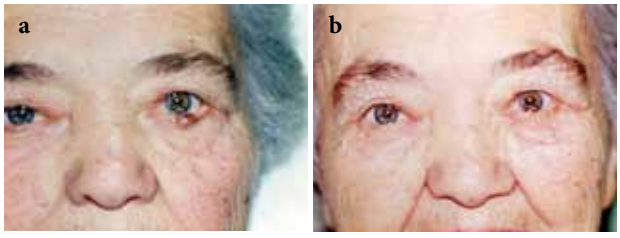


**Figure 4.** A patient with a basal cell carcinoma of the lower eyelid (a) one month after wedge excision of the tumour with direct closure of the defect with tissue advancement (b).

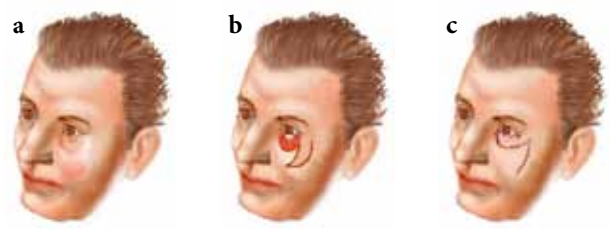


**Figure 5.** Schematic view of a tumour of the lower eyelid (a), placement of a composite mucocartilaginous graft of the nasal septum to restore the deep lamella of the lid (b) and closure of the defect with a Langebeck flap (c).

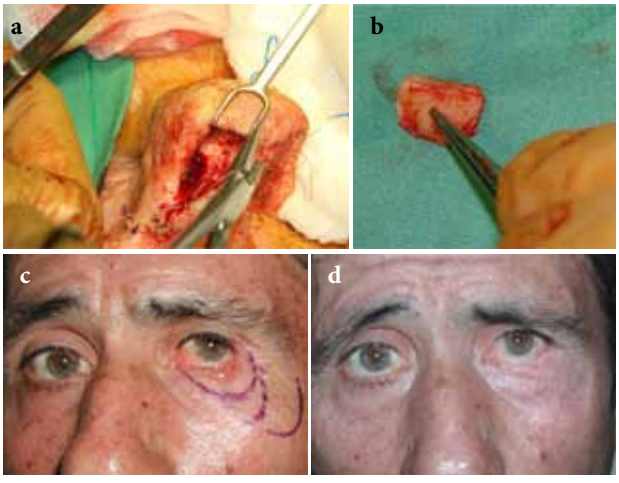


**Figure 6.** Harvest of the composite mucocartilaginous graft of the nasal septum (a,b) and planning of the Langebeck flap (c) in a patient with a basal cell carcinoma of the lower eyelid requiring full thickness excision. The same patient two months after the operation (d).

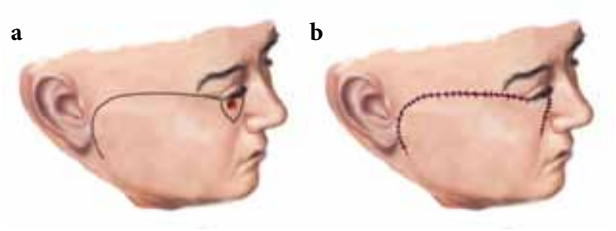


**Figure 7.** Schematic view of planning of excision of a lower eyelid tumour (a) and reconstruction with an Esser rotational flap (a, b).

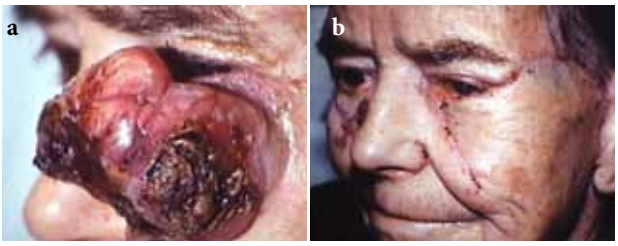


**Figure 8.** A patient with a basal cell carcinoma of the lower lid and cheek (a) and the same patient three weeks after excision of the tumour and reconstruction with a Esser rotation flap.

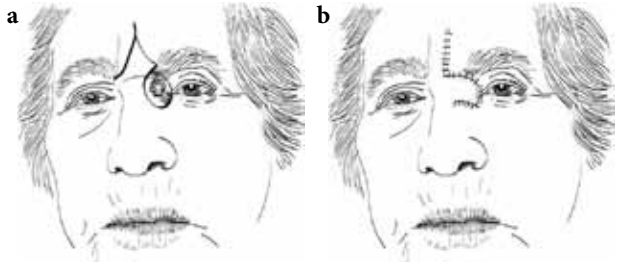


**Figure 9.** Schematic view of planning of excision of a medial canthus tumour (a) and reconstruction with a glabbelar flap (a, b).

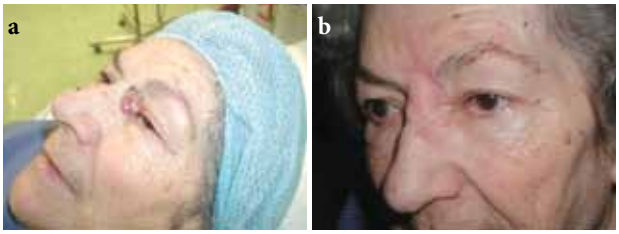


**Figure 10.** A patient with a basal cell carcinoma of the medial canthus (a) and the same patient one month after excsion of the tumour and reconstruction with a glabbelar flap (b).

margin of a defect.[9] The latter was a good option for combined medial canthus and lower lid defects in 8 patients (Figures 11 and 12).

The use of a skin graft was an acceptable reconstruction option for large superficial defects of the lids or medial canthus defects in 7 cases.[10] A skin graft was taken from the contralateral upper eyelid, or from the postauricular or preauricular area for the restoration of the medial canthus (Figures 13 and 14).

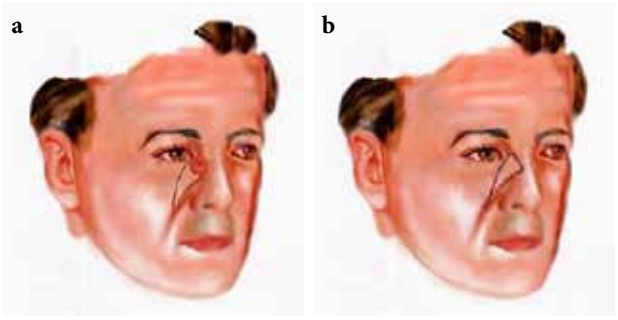


**Figure 11.** Schematic view of planning of excision of a tumour of the medial canthus and lower eyelid (a) and reconstruction with a V to Y advancement flap (a, b).

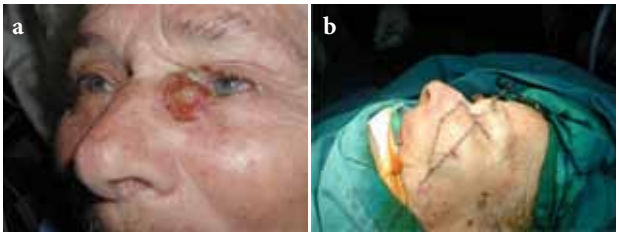


**Figure 12.** A patient with a basal cell carcinoma of the medial canthus and lower lid (a) and the immediate result after excision and reconstruction with a V to Y advancement flap (b).

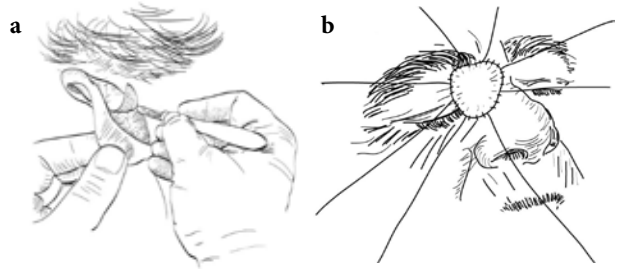


**Figure 13.** Schematic view of harvesting a full thickness skin graft (a) to reconstruct a defect of the medial canthus (b).

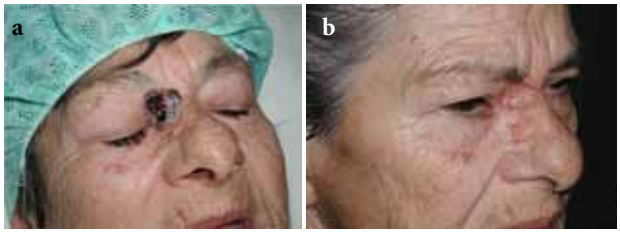


**Figure 14.** A patient with a basal cell carcinoma of the medial canthus (a) one month after excision of the tumour and reconstruction with a full thickness skin graft (b).

The Fricke supraorbital musculocutaneous flap had been used in 3 cases for reconstruction of the upper and lower lid in order to restore the superficial lamella of the eyelids. When a structural support was needed a composite graft of the nasal septum replaced the deep lamella of the lid (Figure 15).

Finally, after a major surgical excision of both eyelids and globe exenteration, a large transposition flap of the forehead[1,7] was used to restore the missing tissue in one patient (Figure 16).

In 9 cases (17%), from whom 7 cases had been operated previously elsewhere, the surgical margins were locally involved. In most cases, scar tissue hindered the intraoperative assessment of the tumour borders. Totally, 7 reoperations were performed for involved margins, all patients having metatypical basal cell carcinoma, which is known for its locally infiltrative growth and absence of clinically clear borders.

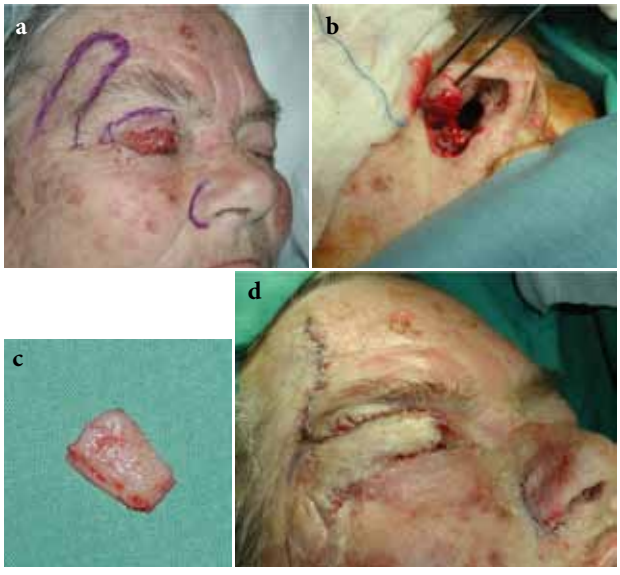


**Figure 15.** Planning of a Fricke flap in a patient with a basal cell carcinoma of the upper eyelid (a). Nasal ala detachment for better exposure of septal cartilage (b) and harvest of mucocartilaginous graft (c). The immediate result after excision of the tumour and reconstruction with a mucocartilaginous graft and a Fricke flap.


**Figure 16.** A patient with a large basal cell carcinoma invading the eye globe (a) after excision of the tumour, global exenteration, reconstruction with a forehead flap and skin grafting of the secondary defect (b).

## DISCUSSION

When reconstructive surgery of the eyelids is planned, various parameters should be considered A very important parameter for the eyelid reconstruction is whether the defect is full or partial thickness with reference to the missing tissue.[5] Partial thickness refers to an excision of tissue that does not penetrate the orbital septum while a full thickness defect concerns all the thickness of the lid with excision of the conjunctiva as well. The second parameter to consider in the eyelid reconstruction is the exact anatomic site of the eyelids which can be separated into four distinct periocular zones. These are the upper eyelid, lower eyelid, medial canthus and lateral canthus all with individual anatomic, functional and aesthetic considerations. Finally, the size of the defect that results after skin cancer excision is another parameter that should be taken into consideration.

Partial thickness defects of the upper and lower lid can be closed primarily if the size of the excised tissue does not exceed 25% of the lid length.[8] If the defect is larger, a full thickness skin graft from the contralateral upper eyelid is the option of choice, while local tissue advancement is always possible for the reconstruction of the lower lid (cheek advancement flaps). A transposition flap from the upper eyelid is also possible for large partial thickness defects of the lower eyelid.

Full thickness defects of the eyelids can also be closed primarily if they do not exceed 25% of the lid length.[8] Primary closure for defects of 50% of the lid length is possible for the lower lid if lateral cantholysis is included. Larger defects require reconstruction of the deep and superficial lamella of the lids. The structural support of the lid margin consisting of the tarsal plates has to be replaced as well which in the majority of the cases is restored with the use of a composite mucocartilaginous graft for both tarsus and conjunctiva restoration.

Defects of the lid margin almost always require a full thickness excision even if the defect is slight because of the proximity to the conjunctiva of the lid.[5,8] Reconstruction of the medial canthal area is achieved with local flaps or a full thickness skin graft while the lateral canthal area is reconstructed with local flaps.

Procedures to eyelids and the periocular area have always been a challenge for the reconstructive surgeon because of their central role to facial appearance. One of the main properties of the lid is to protect the globe and ensure a well covered and moist environment for the cornea. The reconstruction options used had as a main priority the normal proportions of the eye[11] so that no major discomfort would remain to the patient. Exact face metrical analysis and correct presurgical planning ensure that reconstruction options will offer the best result. After all, a good reconstruction plan should ideally take into consideration the subsequent scar contracture, tissue expanding ability and the role of gravity over time.

Pentagonal excision, especially of the lower eyelid, can be achieved for larger lesions to elderly patients reaching even 50% of the lid with direct closure or with a small amount of tissue advancement.[5,8] In addition to the excess of the lid length, older patients often have very loose cheek skin, so that there is no need for secondary defect reconstruction after the use of an Esser rotation flap.

A Langebeck flap has always provided a good result for total lid reconstruction, restoring the missing tissue with a transposition flap, perpendicular to the lid defect, so as to avoid lid retraction (ectropion of the lower lid) and bringing the amount of tissue needed from an area (e.g. the cheek) with abundant skin.[6,7]

The glabellar flap for the medial canthal area is preferably left as a second choice reconstruction plan after the full thickness skin graft if the excision margins are not completely clinically clear during the excision of a malignant lesion.[3,8] This is an axial flap of the contralateral supratrochlear artery, the same artery of the median forehead flap which won't be available for future reconstruction of a wider defect after a possible recurrence of a lesion.

A V to Y flap has always yielded good aesthetic and functional results after the restoration of the lower medial canthus and lid if care is taken to design the flaps axle diagonally and not vertically in order to avoid postoperative ectropion.[9]

## CONCLUSION

Excision of skin cancer of the eyelids is always a demanding procedure where adequate margins and optimal aesthetic and functional outcome are expected while leaving very little space for reoperations. Traditional methods and reconstruction options of the eyelids can always produce good results after proper presurgical planning in order to make maximum use of the local tissues of the periocular area.

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HELLENIC SURGICAL ONCOLOGY 2014; 5(3): 134-139

CASE REPORT

# Chylous leakage after breast-conserving surgery and axillary lymph node dissection for breast cancer

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## ABSTRACT

**Chyle leakage is caused by injury of the thoracic duct, usually caused by trauma or as complication after neck, chest, or abdominal surgery. Only rarely does it occur in association with breast surgery. The diagnosis usually includes the presence of a milky fluid in the axillary drain, the nature of which is confirmed by its biochemical profile. Most cases respond to conservative treatment, while reoperation is reserved for persistent, high volume leaks. Herein, we present a case of chyle leakage in a 55-year old woman with breast cancer who had undergone breast conserving surgery and axillary dissection. The chyle leakage was successfully managed conservatively. We also review the literature for similar cases of this rare condition and discuss the potential mechanism of trauma to the major lymphatic vessels responsible for the chyle leak, diagnostic modalities, as well as criteria and treatment options.**

**KEY WORDS:** breast surgery, axillary lymph node dissection, chyle leakage

## INTRODUCTION

Chyle leakage is caused by injury of the thoracic duct, or its tributaries, and may occur either due to trauma, or as a complication of surgery in the neck, chest, or abdomen.[1-3] Neck dissection, mediastinal and esophageal surgery, as well as abdominal aortic aneurysm repair, represent the most common causes of postoperative chylous fistula, the overall incidence of which is 1-4%.[1,2]

Various systemic complications associated with chyle leak, chiefly fluid, electrolyte and metabolic derangement, as well as comprised immunity have been reported.[2] Sustained leak may lead to hypovolemia, hyponatremia, hypocalcemia and metabolic acidosis.[2] Moreover, the loss of lipids, mainly triglycerides, can potentially cause fat-soluble vitamin deficiency.[2] Fluid shifts and increased metabolic demand may also occur as a result of protein loss, since the chylous fluid transports a large quantity of the total body protein.[2] Apart from malnutrition, this latter fact may institute a depletion of T-lymphocytes and associated attenuation of the cell-mediated immunity, contributing to an increased risk of sepsis.[2] Unless treated, chyle leak may reach a mortality rate of 12.5-50%.[4] Local

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effects with clinical significance such as delayed wound healing, necrosis of the skin flap and even carotid damage following neck dissection, have been reported,[2] while the obvious consequences of increased hospital stay and the delay of adjuvant therapy,[4] should be stressed.

Unlike lymphatic leaks, which are relatively common (17.5%),[3] chylous leak after axillary lymph node dissection in the context of either modified radical mastectomy or breast conserving surgery for breast cancer is potentially rare, since the axilla is anatomically remote from the thoracic duct.[1,4] In this study, we report a case of chyle leakage after breast-conserving surgery and axillary dissection, review the literature, and discuss the potential mechanism of injury, diagnostic means, and management options of such a chylous fistula.

## CASE REPORT

A 55-year-old post-menopausal female was referred to our clinic for surgical management of breast cancer. Her medical history included chronic hepatitis B and arterial hypertension. The patient presented with a palpable hard mass in her left breast posterior to the areola which she had palpated herself six months earlier, as well as associated periareolar skin thickening and nipple retraction. Mammography revealed a spiculated 2.7×1.5 cm BI-RADS 5 mass without enlarged axillary lymph nodes, while FNA from the breast mass was positive. The patient underwent central quadrantectomy with nipple removal (breast-conserving surgery), and level II axillary dissection, as pathologically enlarged lymph nodes were detected intraoperatively. Two drains, one to the quadrantectomy bed and one to the axilla, were inserted. The operative procedure was uneventful.

Pathologic examination revealed a 2.8 cm, Grade II infiltrating ductal breast adenocarcinoma. Stainings for oestrogen and progesterone receptors were strongly positive, while staining for HER-2 was negative. The staining for Ki-67 was positive in 8-10% of the malignant cells. Seven of the 22 excised axillary lymph nodes, the largest of which sized 1.7 cm, had extended metastatic tumour deposits.

From the first postoperative day, a milky fluid was observed in the axillary drain (Figure 1) which was suggestive of chyle, both clinically and biochemically. A low fat diet was instituted, and the axillary surgical site was covered with compression dressing. The breast drain output remained low and the drain was removed on the fourth postoperative day, while the axillary drain output increased up to 150 ml/day on the seventh postoperative day (Table 1). The subsequent gradual reduction of

**Figure 1.** Chyle in the vacuum drain.

**Table 1.** Breast and axillary drain output.

| Post operative day | Breast drain (ml) | Axillary drain (ml) |
|---|---|---|
| 1st | Trace | 50 |
| 2nd | 30 | 110 |
| 3rd | Trace | 100 |
| 4th | 30 | 80 |
| 5th | - | 80 |
| 6th | - | 150 |
| 7th | - | 150 |
| 8th | - | 130 |
| 9th | - | 90 |
| 10th | - | 110 |
| 11th | - | 80 |
| 12th | - | 100 |
| 13th | - | 45 |
| 14th | - | 30 |

output led to the removal of the axillary drain on the fourteenth postoperative day.

After fourteen days of hospitalization, the patient was discharged and was subsequently reviewed in an outpatient setting. The wound was healing well, while no seroma formation was observed. After discussion in the multidisciplinary oncology team meeting, it was concluded that the patient commence adjuvant chemotherapy followed by breast and axillary radiotherapy as well as hormonal therapy.

## DISCUSSION

As axillary dissection is not associated with the anatomic area containing the thoracic duct and its venous anastomosis, chyle leak after axillary lymph node dissection seems a rather unlikely event.[5] However, it does not represent such an improbable scenario as generally thought. Thorough literature review revealed 38 such cases, including the present one (Table 2). The vast majority (36) referred to cases of axillary dissection in the context of breast cancer, while one case[12] concerned a patient with melanoma. In several series of axillary lymph node dissections, the reported incidence of chyle leakage was 0.32% (6/1863),[1] 0.36% (4/1096),[8] 0.47% (4/851)[15] and 0.68% (6/882).[11]

The exact cause of chylous leakage after axillary dissection remains largely obscure.[8] It has been hypothesized that variation in the anatomy of the thoracic duct, may render this major lymphatic

**Table 2.** Cases of chyle leakage after axillary lymph node dissection reported in the literature.

| Reference | Year | N | Site | Breast surgery | ALND level | Treatment |
|---|---|---|---|---|---|---|
| Present case | 2015 | 1 | Left | BCT | II | Conservative[a,c] |
| Thang et al[6] | 2014 | 1 | Left | Mastectomy | NA | Surgical[h] |
| Chan et al[7] | 2013 | 1 | Left | Mastectomy | II | Conservative[a,c] |
| Singh et al[1] | 2011 | 6 | Left | Not recorded | II (3), NA (3) | Conservative (3)[a,e], surgical (3)[f,g,i] |
| Zhou et al[8] | 2011 | 4 | Left | Mastectomy (3), BCT (1) | I, II | Conservative (3)[a,b,c], surgical (1)[f] |
| Taylor et al[9] | 2011 | 1 | Left | Mastectomy | III | Conservative[d] |
| Curcio et al[10] | 2009 | 1 | Left | BCT | NA | Conservative[a] |
| Cong et al[11] | 2008 | 6 | Left (4), Right (2) | Mastectomy | I-III | Conservative[a,c] |
| Sales et al[12#] | 2007 | 1 | Left | | III | Conservative[d] |
| Sakman et al[13] | 2007 | 1 | Left | Mastectomy | I, II | Conservative[a,c] |
| Donkervoort et al[5] | 2006 | 1 | Left | BCT | I-III | No special measures |
| Haraguchi et al[14] | 2006 | 1 | Left | Mastectomy | I, II | Surgical[f,h] |
| Abdelrazeq et al[3] | 2005 | 1 | Left | BCT | I-II | Conservative[a,b,c] |
| Nakajima et al[15] | 2004 | 4 | Left | BCT (3), mastectomy (1) | I, II, I-III | No special measures |
| Purkayastha et al[4] | 2004 | 1 | Left | Mastectomy | I-III | Initially conservative[a], later surgical[f,g] |
| Caluwe & Christiaens[16] | 2003 | 1 | Left | BCT | I, II | Conservative[a,b] |
| Rijken et al[17] | 1997 | 5 | NA | NA | NA | Conservative[e] |
| Rice et al[18] | 1994 | 1 | NA | Mastectomy | NA | Conservative[a] |

N: Number of patients, BCT: breast conservative surgery, NA: data not available, ALND: Axillary Lymph Node Dissection, #: Melanoma patient, a: dietary control, b: adequate drainage, c: pressure dressings, d: stop suction on drain, e: vacuum drain, f: lymphatic ligation with suture, g: muscle fiber transposition, h: glue, i: clips.

channel susceptible to injury during the procedure.[3,15,18] According to several anatomical studies though, the duct has an aberrant course in 20% of cases, and this variation occurs within 1 cm of the jugulovenous junction.[1] Since the distance between the jugulovenous junction, and the deep border of the level III axillary dissection is about 3 cm[1] -reported to be as much as 4-5 cm by some authors[15]- it is highly unlikely that injury to the duct itself may explain the mechanism of injury.[1] Injury to the subclavian duct, or its tributary, has been proposed as a more realistic scenario, as its formation is rather inconsistent and occurs in the central or apical axillary region, the area where level II and III axillary clearance dissection is performed.[1] Only rarely does the subclavian duct join the thoracic duct so as to allow chyle leak to ensue from its injury, provided the junction is valveless, to allow retrograde passage of chyle from the thoracic to the subclavian duct (Figure 2).[1] The potential division of the thoracic duct at its upper part into a right and left branch,[11] or the extremely rare occasion of a right-sided thoracic duct[1] offer a potential explanation for the two cases of chyle leak on the right side, as shown in table 2.

Due to the preoperative and intraoperative fasting state, damage of either the thoracic duct or its main branches is rarely diagnosed intraoperatively, since the above structures are collapsed and their contents blend with the surrounding serous fluids.[19] In the rare occasion of intraoperative detection, the leak may be revealed as an accumulation of clear or milky fluid with a greasy feel on the surgeon's glove.[4] In this case, every possible effort to seal the defect should be made.[4] Typically, as in our case, chylous leakage is evident as drainage of a "milky" fluid postoperatively, and can be confirmed by biochemical analysis of its fat, protein and electrolyte content.[7,8] The leakage volume might be exacerbated after consumption of a full-fat diet, and disappear after cessation of oral intake.[8] Systemic symptoms such as dyspnea, chest pain, and tachycardia, may also accompany a chyle leak.[2] Specialized radiologic examinations, such as x-ray lymphography,[4] computed tomography,[3] lymphoscintigraphy,[3] magnetic resonance

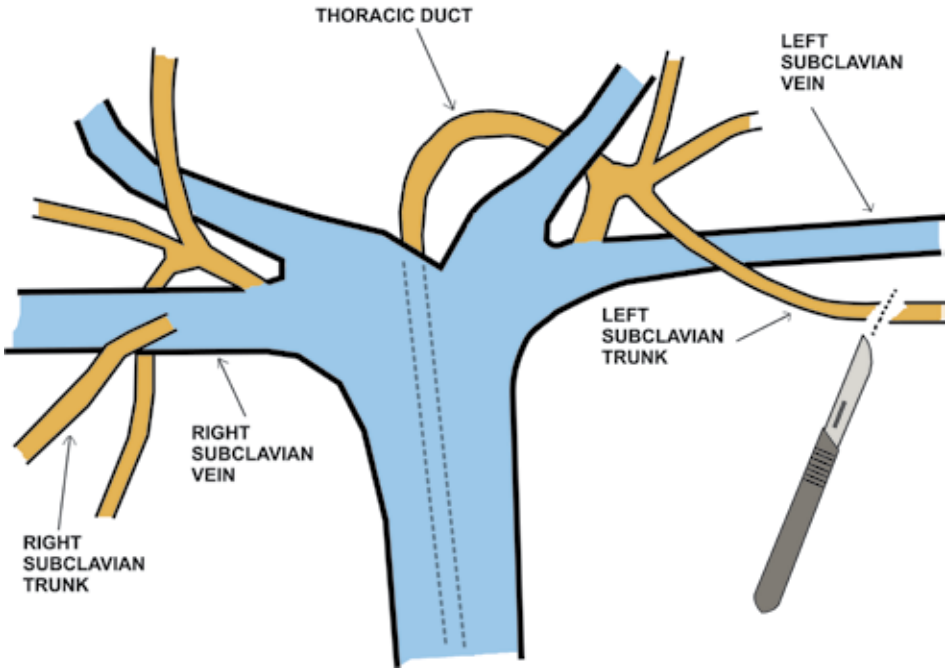


**Figure 2.** Schematic view of drainage of the left subclavian duct into the thoracic duct and potential point of intraoperative damage.

lymphography,[3] SPECT/CT lymphoscintigraphy,[6] as well as ingested labeled fatty acids,[4] may also aid the diagnosis.

Although most of our experience is based on case reports, there is a general consensus that conservative treatment for chylous leakage should be initially instituted.[1,4,5,7] The main objective parameters of conservative treatment include reduction of chyle production and provision of mechanical support to the axillary bed in order to reduce the leak. Cessation of oral intake and total parenteral nutrition were initially advocated,[4,5] while less rigid dietary measures such as enteral feeding with medium chain triglycerides,[5,7] a low fat diet,[1,7] or even no specific dietary control,[5,15] were subsequently reported. Additional measures include pressure dressings, bed rest, elevation of the head and closed drainage,[4,5] while octreotide and tetracycline hydrochloride administration, have occasionally been reported.[7] The majority of the chylous leaks cease spontaneously with the above mentioned measures.[4] The chief criteria for surgical intervention include metabolic complications due to the leak, leakage persistence for more than two weeks, and leakage volume of more than 1 litre after one week,[19] while a lower drainage volume threshold of 500-600 ml has also been reported.[1] However, early reoperation, based on the minimal risk associated with axillary re-exploration, and the avoidance of the delay of subsequent oncologic treatment, has also been advocated.[7] Localization of the leak might be facilitated by preoperative or intraoperative administration of cream or methylene blue through a nasogastric tube.[18] Among the various techniques used are gel foam, oxidized cellulose, or methyl-2-cyanoacrylate application, and tetracycline instillation.[1] Other surgical procedures such as mass ligatures and muscle fibre transposition- including sternomastoid and pectoralis major muscle flaps- thought to induce fibrosis and resultant leak seal, have also been considered.[1] Chyle leakage in our patient was successfully managed with conservative treatment. This successful outcome with conservative management applied to the majority of the presented cases as shown in table 2.

With the above mentioned data, the ability to predict such lymphatic injury preoperatively[7] would be appealing though this has proven extremely controversial.[1,11,15] No disease-associated factors, such as primary tumour size, nodal metastases, or neoadjuvant chemotherapy posed specific risk for the development of chyle leaks according to some authors.[1,15] On the contrary, other authors claimed that extensive axillary nodal metastases, as in our case, exhibited a predisposition to chyle leakage.

In conclusion, chyle leak as a complication of axillary dissection is extremely rare and can usually be managed conservatively. Careful dissection and ligations in the levels II and III may help prevent this complication, especially in patients with extensive nodal metastases.

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HELLENIC SURGICAL ONCOLOGY 2014; 5(3): 140-146

CASE REPORT

# Granulosa cell tumour of the ovary

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## ABSTRACT

**Granulosa cell tumour of the ovary is a rare malignancy that is usually diagnosed at an early stage. Concomitant endometrial pathology is common due to its estradiol production. In the vast majority of patients the tumour is confined to the ovary at the time of diagnosis. A case of a large adult type granulosa cell tumour of the ovary is described and its clinical presentation and management are discussed. The mainstay treatment is surgery. Granulosa cell tumour of the ovary is generally associated with an excellent overall survival, but its potential indolent malignant course and late recurrences, sometimes more than 5-10 years after initial treatment, dictate prolonged surveillance. Bearing in mind various risk factors of recurrence, a multi-disciplinary team may recommend adjuvant systemic chemotherapy.**

**KEY WORDS:** granulosa cell tumour of the ovary, surgery, chemotherapy

## INTRODUCTION

Ovarian granulosa cell tumours are uncommon neoplasms that arise from the sex-cord cells of the ovary and represent 2% to 5% of all ovarian cancers.[1,2] They are divided in two subgroups based on clinical presentation and histological characteristics: juvenile and adult granulosa cell tumours. The majority of the patients are adults, but 5% are (pre)pubertal. The juvenile form is diagnosed in patients younger than 20 years of age in 80% of the cases.[3] The adult type is rarely found in children. Since nearly all granulosa cell tumours are hormonally active and estradiol producing, the majority of young children exhibit signs of precocious pseudopuberty, while the older patients usually present with menstrual irregularities.[3] Granulosa cell tumours of the ovary are bilateral in only 3% of the patients and in the vast majority of cases are confined to the ovary at the time of diagnosis (FIGO stage I).[1,2] In general, its prognosis is excellent. The natural history of these neoplasms is generally one of slow growth, with a tendency towards late recurrence.[1,2,4-6]

Herein, a case of a large adult type granulosa cell tumour of the ovary is described and the clinical presentation and its management are discussed.

## CASE REPORT

A 46-year old morbid obese woman (body mass index 50 kg/m$^2$), with a history of Caesar-

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ean section, appendectomy and heavy smoking behaviour, presented with a large intra-abdominal tumour. During the last six months, she had experienced metrorrhage and menorrhagia. Two months before admission, she suffered from pain in the right abdominal area for four days, while during the month prior to admission, she had experienced constipation and frequent miction. At clinical examination, a large, painless, well circumscribed and mobile mass was found in the right abdominal area, reaching from the pelvis to above the umbilicus. Vaginal examination did not reveal any pathology. Laboratory tests demonstrated only mild anaemia (Hb 11 g/dL). Ultrasonography had shown, besides gall bladder stones, a well circumscribed solid mass of 15.5 cm in diameter in the right abdominal area. Computed tomography had demonstrated a large, solid, well circumscribed mass, measuring 22×13×17 cm, from the origin of the inferior mesenteric vessels to the right parauterine space (Figure 1). The mass showed central necrosis and locally strong and heterogeneous contrast enhancement, while it was in contact with small bowel loops and sigmoid colon, while it caused an imprint in the fundus and the posterior wall of the, at imaging, normal uterus. The organs of the upper abdomen did not show additional pathology. Specifically, liver metastases were not seen. The radiologist concluded that the differential diagnosis of this mass included a gastrointestinal stromal tumour and an adnexal mass.

At laparotomy with a midline incision, a well circumscribed and mobile mass, approximately

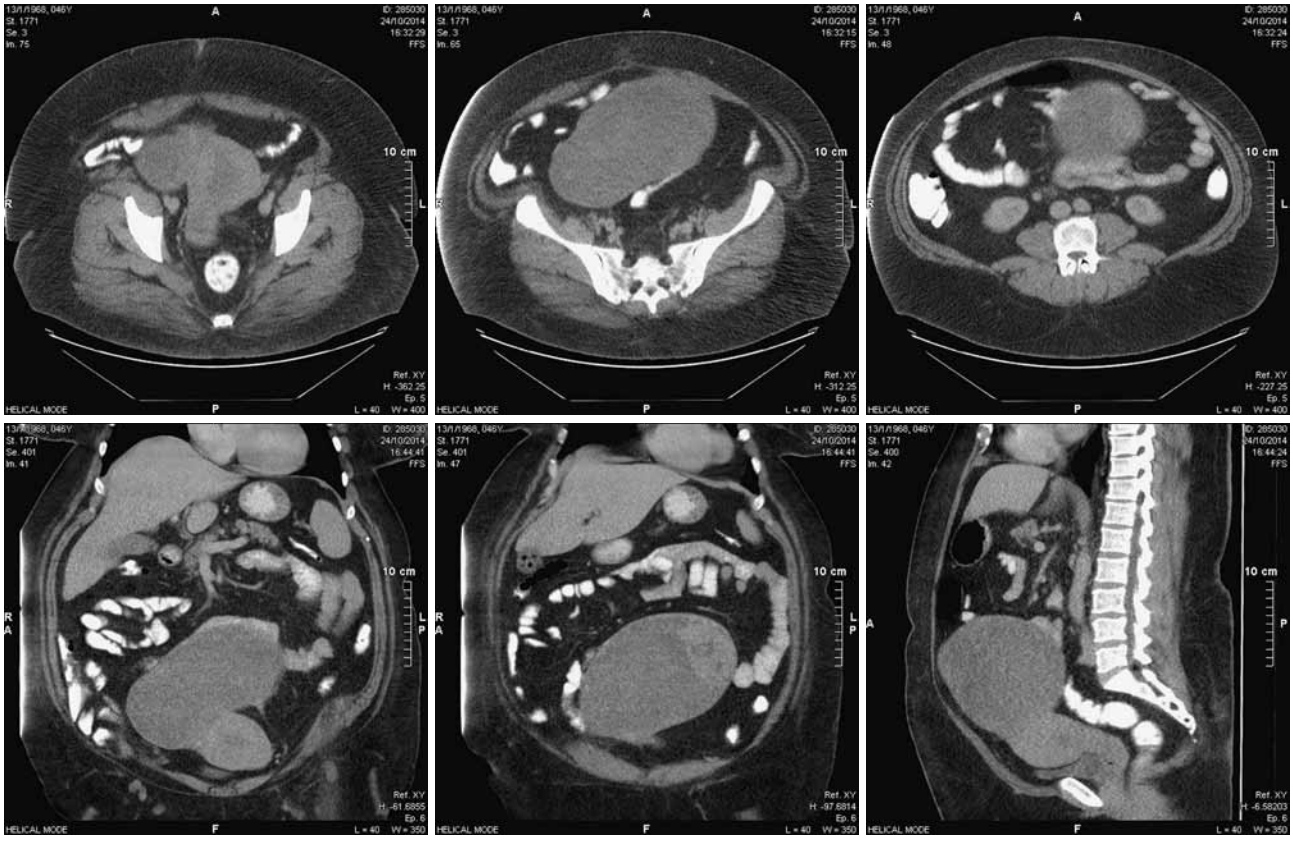


**Figure 1.** Computed tomography of the large intraabdominal tumour, showing central necrosis and locally strong and heterogeneous contrast enhancement, reaching from the mesenterial root to the right parauterine space, adjacent to small bowel loops and sigmoid and causing an imprint in the uterus.

25 cm in diameter, originating from the right ovary and attached to the uterus was found (Figure 2). No other pathology was observed. In the absence of the ability of frozen section biopsy, the tumour was intraoperatively staged as for a malignant adnexal tumour. After wash cytology was obtained, hysterectomy with en block removal of the adnexes and the tumour was performed. Subsequently, a staging omentectomy and multiple peritoneal biopsies were carried out. The postoperative course was uneventful. Cytology was negative for tumour cells. Histological examination revealed an adult-type granulosa cell tumour of the right ovary (Figure 3). The mass was delineated by an intact capsule, had a smooth surface, was 24 cm at its maximal diameter and presented considerable heterogeneity in its mitotic rate (mitotic count ranging per region from 1 to 8 mitoses per 10 microscopic optical field, x400, and Ki67 varying from 3% to 20%). Immunohistochemically, the neoplastic cells were positive for Inhibin and negative for cytokeratine 7 and WT-1 protein, while histochemistry with Gomori staining demonstrated absence of expression between the neoplastic cells. The tumour cells were of medium size, showed moderate pleomorphism and demonstrated various growth patterns, including solid, diffuse, trabecular, islet-like and macrofollicular. In addition, Call-Exner body like structures were observed. In less than 5% of the cross section surface, tubular formations suggestive of Sertoli cell differentiation were observed. Extensive haemorrhagic necrosis was also documented especially at the centre of the specimen. The contralateral ovary and fallopian tube did not reveal significant pathology. The endocervix showed features of chronic cervicitis, whereas the endometrium exhibited simple hyperplasia and a 2 cm endometrial polyp. Peritoneal biopsies and omentum were free of disease. Hence, the granulosa cell tumour was staged as IA.[7]

A multi-disciplinary team discussion suggested measurement of estradiol level as a prognostic marker, staging of the disease by computed tomography and, when staging had been negative for metastatic disease, adjuvant systemic chemotherapy because of the high risk of recurrence. The estradiol level was low (14 pg/ml). Postoperative computed tomography of the chest and the abdomen did not reveal residual or metastatic disease and the patient started adjuvant systemic chemotherapy with cisplatin and etoposide two months postoperatively.

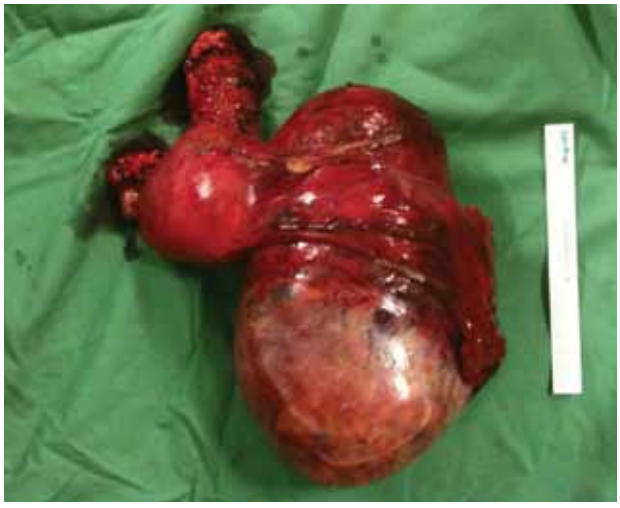

**Figure 2.** The surgical specimen of the right adnexal mass and the uterus and left adnex.

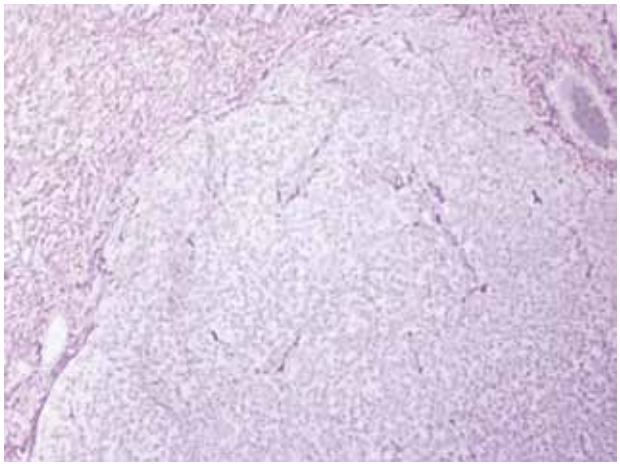

**Figure 3.** Histological examination revealed a granulosa cell tumour of the right ovary. Gomori stain (x100) shows absence of staining among the neoplastic cells.

## DISCUSSION

Adult type granulosa cell tumour of the ovary generally presents in the peri- and postmenopausal women, with a median age at presentation of approximately 50 years and a span from 40 to 70 years of age.[1,2,4,5,8] Its incidence is approximately 1 per 100.000 women per year.[1] The most common presenting symptoms of a granulosa cell tumour of the ovary are abnormal uterine bleeding due to its estradiol production and pain due to its large size.[1,2,4,5] In the reproductive age group, patients may have menstrual irregularities, menorrhagia, intermenstrual bleeding or amenorrhea, while in postmenopausal women, abnormal uterine bleeding may be the presenting symptom. In approximately 10% of the patients, the tumour is either discovered at the time of surgery for abnormal bleeding or diagnosed only after histological examination of the surgical specimen, as in our case. However, the patient's history of metrorrhagia and menorrhagia should have drawn our attention to the possible diagnosis of granulosa cell tumour of the ovary preoperatively. Because of the endogenous estradiol effect, endometrial hyperplasia is frequently present (25-30%), as found in our case, and less frequently endometrial carcinoma is observed at histological examination (5-13%).[1,9] This endometrial pathology is often found only at surgical staging for the ovarian tumour. Endometrial carcinoma related to granulosa cell tumour of the ovary is usually well differentiated, at an early stage and associated with a good prognosis. In very rare cases, Fallopian tube carcinoma may be associated with granulosa cell tumour of the ovary.[10] Increased levels of endogenous estradiol may also cause breast enlargement and tenderness. Patients may describe persistent, localized abdominal or pelvic pain, sometimes with abdominal distension from a large mass. The average size of this tumour is approximately 10 cm, with 50% of cases measuring between 7 and 15 cm.[1,4] Despite the very large tumour size, it remains remarkable that our patient did not notice abdominal distension or a mass but most probably, this could be attributed to her morbid obesity. Acute pain may result from ovarian torsion or tumour rupture.[1,2] In our patient, constipation and frequent miction most likely resulted from the local pressure of the large mass. Most patients have a palpable abdominal or pelvic mass at physical examination.[1,2]

Imaging findings in adult type granulosa cell tumour of the ovary vary widely and range from solid masses to tumours with varying degrees of haemorrhagic or fibrotic changes, to multilocular cystic lesions to completely cystic tumours.[11,12] The estrogenic effects on the uterus may manifest as uterine enlargement or as endometrial thickening or haemorrhage. In our case, no uterine pathology was seen on computed tomography.

In our patient, the diagnosis was established after surgery, the primary treatment modality of granulosa cell tumour. Surgical treatment has traditionally been quite similar to that used for epithelial ovarian cancer.[1,2,6] Every effort should be made to keep the encapsulated mass intact during removal. While the vast majority of these tumours are confined to the ovary, the staging system used for granulosa cell tumours of the ovary is the one applied for epithelial ovarian cancer (FIGO staging system). Surgical treatment and staging at the time of initial diagnosis is important for prognosis as well as likelihood of (local) recurrence and includes cytology of ascitic fluid or peritoneal lavage fluid, hysterectomy with bilateral salpingo-oophorectomy, removal of peritoneal lesions or, if no macroscopic multiple peritoneal disease is present, blind peritoneal biopsies and omentectomy.[1,2,6] If the patient is young and wants to preserve her fertility, and the disease appears to be confined to one ovary, a unilateral salpingo-oophorectomy may be indicated.[1,4,5] However, in the case of fertility preservation, one should assure that there is no concomitant uterine pathology and therefore an endometrial biopsy might be necessary. Pelvic and paraaortal lymphadenectomy may be omitted and is only indicated in the rare case of macroscopically involved lymph nodes.[6]

At histological examination, the granulosa cell tumours vary greatly in gross appearance. Sometimes they are solid tumours that are soft or firm, depending on the amounts of neoplastic cells and fibrothecomatous stroma they contain, and are yellow or grey, depending on the amount of intracellular lipid in the lesion.[1] More commonly, the granulosa cell tumours are predominately cystic and may grossly resemble mucinous cystadenoma or cystadenocarcinoma. They may be well or moderately differentiated. Histologically, there is a proliferation of granulosa cells often with a stromal component of fibroblasts, theca or luteinized cells.[13] The granulosa cells have scant cytoplasm and a round to ovoid nucleus with a longitudinal groove. The mitotic activity rarely exceeds 1-2 per 10 high power fields. When luteinized, the cells develop abundant eosinophilic or vacuolated cytoplasm, and the nuclei become round and lose their characteristic groove. The rare presence of bizarre nuclei does not have an adverse effect on the prognosis. The tumour cells grow in a variety of patterns.[13] The best known of these is the microfollicular pattern characterized by the presence of Call-Exner bodies. Others include the macrofollicular characterized by large spaces lined by layers of granulosa cells, insular, trabecular, diffuse (sarcomatoid) and the moiré silk (watered silk) patterns. A fibrothecomatous stroma often surrounds the granulosa cells. Histochemistry with Gomori staining demonstrates absence of expression between the neoplastic cells. Granulosa cell tumours are immunoreactive for CD99, alpha-inhibin, vimentin, cytokeratin (punctate), calretinin, S-100 protein and smooth muscle actin. The tumour cells are negative for cytokeratin 7 and epithelial membrane antigen.[13] Differential diagnosis includes cystadenomas, undifferentiated carcinomas, adenocarcinomas and carcinoids.[1,2,13]

As already mentioned, in the majority of patients the tumour is limited to the ovary. Dissemination of the tumour is mainly intraperitoneal and very rarely lymphogenous or haematogenous.[1] Despite the large size of the tumour, in our patient the disease seemed to be limited to the ovary. Granulosa cell tumours of the ovary are known for their late, mainly local, recurrences. Although most local relapses are seen in the first few years, it is not unusual to detect such a recurrence after more than 5 to 10 years.[1-6] The 5-year and 10-year recurrence free survival rates are approximately 70% and 35%.[4] Initial FIGO stage higher than 1, tumour rupture, larger tumour size, high mitotic index (≥5 mitoses per 10 high power fields), increased body mass index and the presence of diabetes mellitus have been associated with increased risk of recurrence.[1,2,4,5] Patients with an increased risk of recurrence may benefit from adjuvant treatment. Recently, a nomogram has been developed to predict recurrence free survival at 2, 5 and 10 years and may be helpful in selecting patients for adjuvant treatment.[4] Applying this predictive tool for our patient, the estimated recurrence risk was 50%, 80% and even 100% at 2, 5 and 10 years, respectively. There are no convincing data to support the use of radiotherapy in the adjuvant setting. Its efficacy is unclear, while its toxicity to other organs, i.e. bowel and urinary bladder, may be significant. Postoperative radiotherapy may be indicated after surgery for limited stage II-IV disease.[6] Since granulosa cell tumour of the ovary is a potentially responsive tumour to single agent and combination chemotherapy, postoperative systemic chemotherapy may be advocated in those patients that are at high risk for relapse.[1,2.6] Due to its rarity and the relatively small number of patients in the reported series, firm conclusions regarding the optimal drug regimen cannot be drawn. Usually platinum-based chemotherapy has been administered and the combinations of bleomycin, etoposide and cisplatin and of paclitaxel and carboplatin have been recommended as the preferable regimens.[1,6,7] In our patient etoposide and cisplatin was given, without bleomycine because of her morbid obesity and heavy smoking behaviour. Generally, the available evidence on the effectiveness of different treatment modalities

for the management of adult type granulosa cell tumours of the ovary is very limited because of its rarity, the large variety in treatment regimens and the high risk of bias in the reported studies.[14]

Secondary surgery is the mainstay treatment in case of locoregional recurrence. While at primary presentation, extrapelvic involvement with peritoneal carcinosis appears only rarely, surgical cytoreduction during relapse is more challenging involving a multivisceral approach.[15] The role of radiotherapy in the palliative setting may be appropriate for symptomatic disease which can be encompassed by acceptable toxicity and in those patients who are not suitable for surgery or chemotherapy. Systemic chemotherapy is generally advocated for systemic disease, irresectable relapse or after surgery for locoregional recurrence, although its effectiveness seems to be moderate.[1,2,6,16] Regimens mentioned for the adjuvant setting are preferred, but bevacizumab or leuprolide may be considered for recurrent disease.[6] Recurrent disease may also be managed with hormonal therapy, but experience is limited.[17]

Due to their tendency to recur long after the initial diagnosis, prolonged surveillance is essential and constitutes regular physical examination including pelvic exam, computed tomography as baseline study after initial treatment and for unexplained abdominal symptomatology or hormonal changes, annual chest radiography and the use of tumour marker as available.[1,2,6] Estradiol, inhibin and Müllerian inhibitory substance (MIS) may be used as tumour markers. In our patient immediate postoperative measurement of estradiol was low. Unfortunately, we did not have the ability to measure the other two tumour markers in our hospital.

The overall survival of patients with FIGO stage I granulosa cell tumour of the ovary is excellent with a 5-year and 10-year survival rate of 90-100% and 85-95%, respectively. For FIGO stage II patients these percentages decline to 55-75% and 50-65%, respectively, while the overall survival of FIGO III and IV patients is only 22-50% at 5 years and 17-33% at 10 years.[1]

In conclusion, granulosa cell tumour of the ovary is usually diagnosed at an early stage and concomitant endometrial pathology may be found due to its estradiol production. In the vast majority of patients the tumour is confined to the ovary at the time of diagnosis. The mainstay of treatment is surgery. Granulosa cell tumour of the ovary is generally associated with an excellent overall survival, but its potential indolent malignant course and late recurrences, sometimes more than 5-10 years after initial treatment, constitute prolonged surveillance essential. Bearing in mind various risk factors of recurrence, a multi-disciplinary team may recommend adjuvant systemic chemotherapy in an attempt to reduce the risk of (late) recurrence.

## ACKNOWLEDGEMENT

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

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