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αλλού κι αλλού ξερά τα άχυρα της θημωνιάς,
έτσι σκορπίστηκαν και τα μακριά μαδέρια.
..Κι όμως ο Οδυσσέας κρατήθηκε σ' έναν κορμό,
τον καβαλίκεψε, λες κι ήταν άλογο της κούρσας..
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CONTENTS

HELLENIC SURGICAL ONCOLOGY 2016; 7(3): 124-129

ORIGINAL PAPER

Co-morbidity factors in patients with colorectal cancer
A pilot study

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ABSTRACT

AIM: The purpose of this study was to investigate the co-morbidity factors of elderly patients with colon cancer, as a deviation or postponement cause as to the optimal treatment. MATERIAL AND METHODS: This was an observational epidemiological study. The study involved 40 patients who were hospitalized for surgical treatment due to colon cancer. The entry criteria of patients were to have colon cancer and at least one concomitant disease. The patient's disease was estimated with the Charlson co-morbidity scale and the ASA score. RESULTS: The study sample consisted of 23 (57.5%) men aged 73.1±7.4 years and 17 (42.5%) women aged 71.4±11.2 years. A total of 13 (32.5%) patients had cancer in the right colon, 16 (40.0%) in the left colon and 11 (27.5%) in the rectum. According to the ASA score, 9 (22.5%) patients were healthy (ASA score=1), 24 (60%) had mild systemic disease (ASA score=2) and 7 (17.5%) had severe systemic disease irreversible (ASA score=4). The Charlson co-morbidity score of patients was 2.8±2.6. In 7.5% of patients the surgery was postponed. Co-morbidity was calculated to be 92.5%. The most frequently found co-morbidities were hypertension, diabetes, metastasis, and atrial fibrillation. Patients with cancer in the left colon and sigmoid had significantly lower ASA score relative to the other (1.7±0.6 vs. 2.3±0.6, p=0.028). CONCLUSIONS: Patients with colon cancer who are candidate for surgery have high levels of co-morbidity, especially when the tumour is located in the left colon.

KEY WORDS: colon cancer, co-morbidity, elderly, ASA score, Charlson co-morbidity

INTRODUCTION

Surgical treatment of elderly patients presents complex problems associated with the risk and benefit. For this reason expertise in the treatment of geriatric surgical patients is needed. The perioperative care of geriatric surgical patients is nowadays an emerging topic for many medical subspecialties. With their harmonious coopera-

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tion the best possible and desirable solution for these geriatric surgical patients may be achieved.[1]

Colorectal cancer is one of the most common malignancies worldwide and is among the types of cancer with an increased frequency in elderly patients. According to data from the Greek Society of Digestive Oncology, more than 300,000 new cases are diagnosed each year in Europe, of whom half are estimated to die from this disease.[2] The disease can be prevented by implement of an appropriate preventive programme, which aims not only to detect cancer at an early stage, but also the timely emergence of polyps who are the main condition evolving into cancer.[2] The high incidence and mortality of colon cancer is due to the fact that the screening programs are not largely accepted in healthy population, because of fear for the disease, but also the cost.[3] The result of this is that the patient is treated surgically at a greater age, thus increasing the likelihood of concomitant health problems which are the reason for postponing or deviation from the optimal therapeutic treatment.[3,4]

In developed countries, the life-time risk of an adult to develop colorectal cancer is 6%, meaning that 1 out of 18 adults will be diagnosed with colorectal cancer at a certain time of his or her life. Survival rates depend largely on the stage of the disease. Almost 94% of patients with limited disease survive more than five years, 70% with locally advanced disease patients exceeds more than five years, while only 9% of those with metastases live more than 5 years. Despite the knowledge that the very early diagnosis improves survival, only 35% of cancers are diagnosed early, 38% with locally advanced disease and 22% with metastaseis.[2]

The co-morbidity is a negative factor which affects the outcome to a greater extent on the age patient. In particular, patients with colorectal cancer exhibit higher mortality than those without co-morbidities, regardless of age. Several mechanisms could explain this difference in survival rates. Severe health problems may affect survival regardless of the existence of colorectal cancer. Furthermore, co-morbidity acts as camouflage covering the symptoms of cancer, thereby delaying the diagnosis of colon cancer, the disease progresses to a next stage and prognosis is difficult. Also, the presence of accompanying diseases may prohibit the performance (or extent) surgical treatment of colorectal cancer with poor results for the patient. Finally, it has been observed that the co-morbidity interacts with cancer and accelerate the its development.[5,6]

The aim of this study was to identify the co-morbidity factors of elderly patients with colorectal cancer that causes deviation or postponement of the optimal treatment.

MATERIAL AND METHODS

This is a prospective observational study. The study involved 40 patients who were hospitalized for surgical treatment of colorectal cancer in the University Hospital of Larissa, Greece. For inclusion in the study the patient had to be diagnosed with colon cancer. The co-morbidity of the patients was calculated with the Charlson co-morbidity index scoring system and the ASA score. The ASA score varies from 1 to 6, with a score of 1 representing generally healthy individuals, a score of 2 those with mild systemic disease, a score of 3 those with severe systemic disease, a score of 4 those with severe systemic disease which is a constant threat to life, a score of 5 moribund patients and a score of 6 brain dead patients.[5] Patients were divided into two categories according to their age, in elderly (>70 year) or not (<70 years).[7]

STATISTICAL ANALYSIS

The t-test was used to compare continuous variables, the Mann-Whitney test for non continuous / ordinal variables, and the Chi square test for categorical variables. The distribution of variables was checked by Kolmogorov Smirnoff test. The level of statistical significance in the univariate analyses was set at 0.05. Also, Pearson product-

moment correlations and univariate analysis were conducted to examine the potential relationships between Charlson co-morbidity index scoring system and ASA score and the rest variables of patients. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), Version 21 for Windows.

RESULTS

The demographics data of all included 40 patients are presented in table 1. Thirty-two (80%) patients were admitted on a regular basis, 7 (17.5%) as an extraordinary hospitalization and 1 (2.5%) as an urgent. According to the ASA score, 9 (22.5%) patients were healthy, 24 (60%) had mild systemic disease and 7 (17.5%) had severe irreversible systemic disease. The Charlson co-morbidity score of patients was 2.8 ± 2.6. For a small proportion of patients (7.5%) surgery was postponed due to co-morbidity. The patients underwent colectomy or only creation of a diverting colostomy or ileostomy.

Co-morbidity was observed in 92.5% of the patients Totally, 19 patients (47.5%) had hypertension, 2 (5%) hepatitis, 4 (10%) coronary artery disease, 10 (25%) diabetes mellitus, 6 (15%) atrial fibrillation, 4 (10%) prostatic hypertrophy, 7 (17.5%) metastases, 2 (5%) renal failure, 1 (2.5%) anaemia, 2 (5%) brain aneurysm, 2 (5%) psychiatric disorders, and 2 (5%) a history of a stroke. The results are shown in Table 2.

Women had significantly higher ASA score compared with men (2.2 ± 0.6 vs. 1.8±0.6, p <0.05). Patients younger than 70 years had significantly lower ASA score compared with the other patients (1.7±0.5 vs. 2.1±0.7, p=0.028). The ASA score at cancer diagnosis was 2.3±0.6 in regarding to cancer in cecum and right colon 1.7±0.6 for cancer in the left colon and sigmoid colon and 1.9±0.5 for rectum cancer.

The ASA score has positive linear weak to moderate correlation with age (r=0.449), positive linear weak correlation to age group (r=0.348), positive linear weak to moderate correlation with no history (r=0.429) and negative linear weak correlation with gender (r=-0.309), negative linear weak to moderate association with artery disease

Table 2. Co-morbidity of the patients.

Disease	N (%)
Arterial hypertension	19 (47.5%)
Diabetes	10 (25%)
Metastasis	7 (17.5%)
Atrial fibrillation	6 (15%)
Coronary artery disease	4 (10%)
Prostatic hypertrophy	4 (10%)
Hepatitis	2 (5%)
Renal failure	2 (5%)
Brain aneurysm	2 (5%)
Mental disorders	2 (5%)
History of stroke	2 (5%)
Anemia	1 (2.5%)

Table 1. Patient`s demographics.

	Total	Male	Female	p-value
N	40	23 (57.5%)	17 (42.5%)	0.001
Age	72.3±9.2	73.1±7.4	71.4±11.2	0.574
≤70 years	15 (38%)	8 (53%)	7 (47%)	0.295
>71 years	25 (63%)	9 (36%)	16 (64%)	0.303
Cancer in cecum and right colon	13 (33%)	3 (23%)	10 (77%)	0.001
Cancer in left colon and sigmoid	16 (40%)	9 (56%)	7 (44%)	0.036
Cancer in rectum	11 (28%)	3 (27%)	8 (73%)	0.001

(r=-0.423) and negative linear weak to average correlation to stroke (r=-0.382). The rating in CCISS score had negative linear correlation with patient`s metastases (r=-0.371) and positive linear weak correlation with clean background (r=0.306).

DISCUSSION

The fact that cancer is mainly a disease of older people, and taking into account that the co-morbidity is common among the elderly, it could be generally considered that co-morbidity is common among cancer patients. This finding can be supported for different reasons. First, cancer and co-morbidity share many common risk factors. Age is the most obvious example, but there are many others. Smoking, poor diet, lack of physical activity, obesity and alcohol abuse are all risk factors for a range of common non-malignant conditions, including diabetes, hypertension, respiratory, cardiovascular and peripheral vascular disease and hepatic disease, but also for many cancers including lung, bladder, head and neck, colon, liver and breast cancer.[8] Moreover, co-morbidities can cause cancer. There are a number of chronic diseases, especially chronic infections, immune system diseases and diabetes causally associated with increased risk of cancer. For example, hepatitis B may cause chronic liver disease that is closely associated with hepatocellular carcinoma and tuberculosis patients have an increased risk of lung cancer.[9] In similar results appear to reached in this study, as hypertension and diabetes were the two most commonly reported co-morbidities. Conditions associated with immunosuppression (such as HIV/AIDS) or deregulation of the immune system (such as rheumatoid arthritis) associated with a number of cancers.[10,11] Examples are the HIV/AIDS-related Kaposi's sarcoma, various cancers in patients with Hodgkin lymphoma and non-Hodgkin lymphoma and other haematological malignancies associated with non-Hodgkin lymphoma.[10,11] The precise mechanisms by which these associations could arise have not been fully elucidated, but it is likely to be multifactorial.[10] Diabetes is also associated with an increased risk of many malignancies, including colon, pancreatic, liver, endometrial, and bladder cancer.[10,12,13] While partially these conditions may be associated with common risk factors among diabetes and cancer (such as obesity), there are also indications that there are specific biological pathways directly linking diabetes with cancer.[10,12,13]

Cancer can also cause (co)morbidity. However, this issue is confusing in clinical medicine, since the co-morbidity is usually considered as a cancer complication and not as a co-morbidity condition per se. While diabetes is known to cause cancer of the pancreas, maybe the reverse happens. Cancer of pancreas is the cause of diabetes in a small percentage of cases through the destruction of the islet cells of the pancreas which produce insuline.[10,12,13]

On the other hand, however, the co-morbidities can protect against cancer, either directly or indirectly. As patients with diabetes are at increased risk of developing a number of cancers, they have a smaller risk of developing lung cancer, prostate cancer and Hodgkin's disease.[13] While it is not exactly known why this happens, it is evident that this should be due to changes in hormonal profile, growth factors and steroids. Patients with hypothyroidism have also been found to have lower rates in breast cancer.[10] Treatment for diseases of co-morbidity may also be protective. For example, the use of non-steroidal- anti-inflammatory drugs commonly used in arthritis associated with decreased risk of colon cancer.[14]

While there is general agreement that the co-morbidity is common among cancer patients, it is extremely difficult to state precisely how common is this. This is due to the fact that the prevalence of co-morbidity varies, sometimes dramatically, according to the measure of co-morbidity used, the available data, the study of population and location of the cancer. In assessing the impact of co-morbidity in chemotherapy use and outcomes among patients with solid tumours, the prevalence of co-morbidity has been reported to range among

patients with cancer from 0.4% to 90%.[15] In the present study, the incidence of co-morbidity rate was 92.5%, very high compared to other studies.

It is not surprising that the studies using a more comprehensive measurement of co-morbidity show higher prevalence of co-morbidity than those that use a more restrictive approach. For example, one study used a comprehensive and inclusive approach to identify the co-morbidity in computerized medical records in a group of patients with breast cancer and found that 72% had at least one comorbidity.[16] This is much higher than in another previous study which found that 13% of women with breast cancer had at least one concurrent disorder.[17]

Most studies using the Charlson index indicate that 10-75% of cancer patients have at least one rating in the index Charlson.[18,19] The variation is largely due to the characteristics of the study population and the data collected. For example, studies are limited to elderly patients generally have higher levels of co-morbidity. Co-morbidity also tends to be higher among patients with certain cancers, especially those associated with smoking, such as lung cancer, head and neck cancer and bladder cancer.[20] Studies based on administrative data often (but not always) report lower levels of co-morbidity than those based on medical – clinical reports.[20] In this study 95% of patients had at least one vote in Charlson index, a percentage much higher than the reported in other studies. This difference is likely due to the small sample of the study since it is a pilot study, which will be clarified as soon as the collection of data will be completed and make the final statistical analysis.

Despite these uncertainties, there is universal agreement that the co-morbidity is common among cancer patients. It is less clear whether cancer patients have higher co-morbidity rates than people of similar age without cancer. Some authors have generally found prevalence of co-morbidity among patients with cancer similar to populations without cancer.[21,22] Conversely, other studies have reported that cancer patients have somewhat higher levels of co-morbidity in the general population.[23,24] Two studies compared the self-reported prevalence of diseases in the USA in people with a history of cancer and those who have no history of cancer.[23,24] One study found that among people aged over 65 years, 3.9% of patients cancer reported having three or more chronic conditions, compared with 2.3% of people without a history cancer.[23] Similarly, another study found that with the exception of patients with melanoma, non-Hodgkin's lymphoma and prostate cancer, the cancer patients were more likely to report two or more diseases compared to others.[24] Also there are differences in the estimated prevalence of co-morbidity even within the same malignant diseases. For example, estimation of the prevalence of diabetes among patients with colon cancer is between 6 and 18%, hypertension between 16 and 47%, and chronic respiratory disease between 5 and 22%. These differences are due to the study population, the collection of data and definitions used for specific co-morbidities. Generally it has been shown that co-morbidity in cancer includes hypertension, respiratory disease, heart disease, cerebral vascular disease, history of cancer, arthritis and diabetes. In the present study, patients with colon cancer had high levels of co-morbidity. The most frequently found co-morbidities were hypertension, diabetes, metastasis, and atrial fibrillation.

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HELLENIC SURGICAL ONCOLOGY 2016; 7(3): 130-133

ORIGINAL PAPER

LLETZ Cone biopsy for cervical intraepithelial neoplasia
Analysis of sensitivity and specificity of colposcopy and cytology

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ABSTRACT

AIM: The aim of this retrospective study is to evaluate the results of cytology and colposcopy in relation to the final histological diagnosis of women undergoing Large Loop Excision of the Transformation Zone (LLETZ) cone biopsy. MATERIAL AND METHODS: Patients with abnormal cytology results, at least ASCUS (Atypical Squamous Cells of Undetermined Significance), who were examined at the Oncology Unit of the First Department of Obstetrics and Gynaecology between 2008 and 2014 were included in the study. The sensitivity and specificity of the cytology results and colposcopy were determined for the diagnosis of low grade (LGSIL) and high grade (HGSIL) intraepithelial neoplasia of the cervix in relation to the final histological results. Additionally, the final histological results of the cones, the cone biopsy margins and the frequency of relapse were noted. RESULTS: From the total of 129 patients who underwent colposcopy due to abnormal cytology test results, 63 underwent LLETZ cone biopsy. In 12 (19%) of the 63 patients LGSIL was diagnosed, in 41 (65%) patients HGSIL, in 2 (3%) cases invasive cancer, and in 3 (5%) cases chronic cervicitis, while in 5 (8%) cases no residual disease was found in the cone. The sensitivity and specificity of the cytology for LGSIL lesions were 40% and 75%, and of the colposcopy 90% and 77%, respectively. Regarding HGSIL lesions, the sensitivity and specificity of the cytology results were 41% and 80%, and colposcopy 78% and 80% respectively. The sensitivity of colposcopy was significantly better (p=0.0002). In three patients (4.5%) the cone borders were positive and four patients (6%) showed relapse of LGSIL after a follow-up of 20 months. CONCLUSIONS: Colposcopy is more sensitive than cytology to accurate diagnose cervical dysplasia. LLETZ cervical cone biopsy is a successful treatment method of cervical intraepithelial neoplasia.

KEY WORDS: cervical dysplasia, cervical intraepithelial neoplasia, colposcopy, cytology, LLETZ cone biopsy

INTRODUCTION

The Large Loop Excision of the Transforma-

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tion Zone (LLETZ) cone biopsy constitutes clearly the treatment of choice for cervical intraepithelial neoplasia after having been diagnosed with colposcopy. The method's main advantage is the performance in an outpatient setting with a low bleeding risk and good and immediate cicatrisation.[1] Examination of the removed tissue results in accurate determination of the lesion's pathology, contributing to proper planning of the patient's management.[2] Finally, an equally important advantage in comparison with other therapeutic modalities is the low cost, which in combination with the convenience of the process can sometimes lead to irrational use and overtreatment.[3]

The aim of this retrospective study is to evaluate the results of abnormal cytology, at least ASCUS (Atypical Squamous Cells of Undetermined Significance), and colposcopy findings in relation to the final histological results of the cone biopsy.

MATERIAL AND METHODS

A total number of 129 patients with an age range of 17 to 63 (average age 33 years and standard deviation (SD): ±9.3) underwent colposcopy in the First Department of Obstetrics and Gynaecology from 2008 to 2014. The sensitivity and specificity of the cytology and colposcopy results for low grade (LGSIL) and high grade (HGSIL) intraepithelial neoplasia of the cervix were calculated, comparing the results with the final histology.

RESULTS

Of the total of 129 patients (Figure 1), who had been examined by colposcopy, 76% underwent punch biopsies, while 93% were diagnosed with at least ASCUS cytology. From the total of 129 patients, 63 underwent LLETZ cone biopsy. In 12 (19%) of the 63 patients LGSIL was diagnosed, in 41 (65%) patients HGSIL, in 2 (3%) cases invasive cancer, and in 3 (5%) cases chronic cervicitis, while in 5 (8%) cases no residual disease was found in the cone.

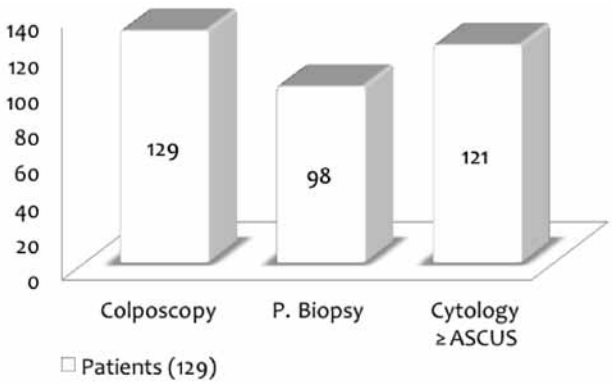

Figure 1. Initial diagnostic approach for the 129 patients.

Regarding the treatment of intraepithelial neoplasia, the therapeutic management included LLETZ cone biopsy (55%), laser vaporization (35%), cone biopsy using a laser device (5.5%) and cone biopsy with a scalpel (4.5%). The average length of the cones was 2.5 cm (SD: ±0.8), the average width 1.6 cm (SD: ±0.7), while the average volume in a total number of 40 cones was 1.5 ml (SD: ±0.5). In 4.5% of the cone specimen the margins were positive for malignant cells, while the recurrence rate was 6%.

The sensitivity of cytology demonstrating the correct (histological) diagnosis was 40% for LGSIL lesions and 41% for HGSIL lesions (Figure 2), while the specificity was substantially higher, being 75% for LGSIL lesions and 80% for HGSIL lesions.[4]

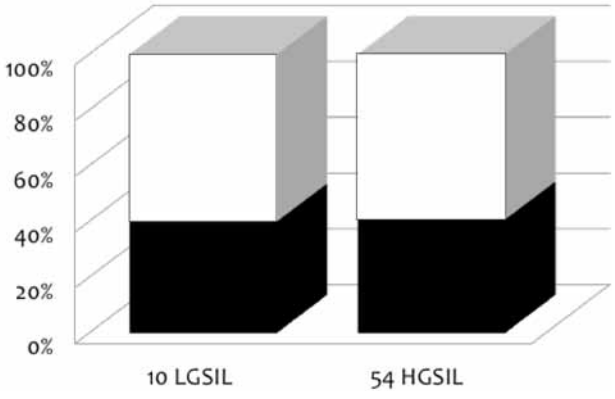

Figure 2. The sensitivity of cytology to detect LGSIL and HGSIL lesions.

On the other hand comparing the sensitivity and specificity rates of colposcopy in relation to the final histological results, a more improved and reliable accuracy was clearly observed.[5] The sensitivity was 90% for LGSIL and 78% for HGSIL (Figure 3), while the specificity was 77% and 80%, respectively.

DISCUSSION

Considering that the cervical cancer is one of the most frequent gynaecological cancers and the second leading cancer cause of death in females, it is clear that it is importance to correctly and timely diagnose and treat even at the CIN level, in order to reduce the invasive cervical cancer rate.[6,7]

LLETZ cone biopsy seems to be a successful method of treatment of cervical intraepithelial neoplasia with less blood loss, good healing, low cost and the flexibility of taking part in outpatient level.[9] A prerequisite for the effectiveness of the cone biopsy is the assessment of the pathological region due colposcopy.[10] The present study demonstrates the higher sensitivity and specificity rate of the colposcopy compared to cytology and particularly for dividing the low from the high grade cervical neoplasia.[9]

This distinction seems very important, based on references which analyze the evolution rate of the low grade to high from 10% to 20% and the change rate from high grade to invasive cancer from 12% to 70%.[11,12] This significant rate of malignancy transformation represents the reason for the investigation of proper and earlier diagnosis and treatment of cervical lesions.[6]

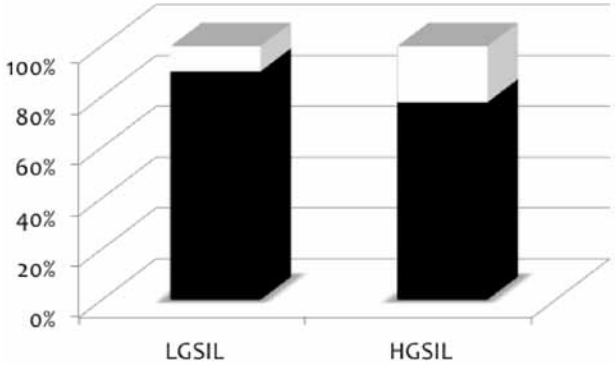

Figure 3. The sensitivity of colposcopy to detect LGSIL and HGSIL lesions.

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REVIEW

Diagnosis of recurrent laryngeal carcinoma after (chemo)radiation and its salvage surgery

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ABSTRACT

The detection of recurrent laryngeal carcinoma after radiotherapy may be difficult due to difficulties in differentiation between recurrent disease and postradiation effects. If laryngeal recurrence after radiotherapy is detected, salvage surgery in selected patients is the only curative treatment option. However, salvage surgery is associated with high complication rates, particularly pharyngocutaneous fistula formation. Aspects of diagnosis and salvage laryngectomy are discussed.

KEY WORDS: laryngeal carcinoma, recurrence, diagnosis, salvage laryngectomy, survival, complications

INTRODUCTION

Squamous cell carcinoma of the mucosal lining, is the most frequent malignancy of the head and neck region, and accounts for 4% of all malignant tumours worldwide. The incidence increases with age, with most patients over the age of 55. More than two thirds of patients with head and neck squamous cell carcinoma (HNSCC) present with advanced stage disease. Laryngeal carcinoma is the most frequent tumour within the head and neck in Europe.[1]

In the treatment of laryngeal cancer preservation of function without compromising chances of cure is challenging. The larynx harbours functions of vocalization, swallowing and respiration. Preservation of an intelligible voice is an important consideration in choosing a treatment modality.

Patients with early-stage disease can very effectively be treated with single-modality larynx-sparing approaches. Small superficial cancers are successfully treated by radiation or surgery alone, including endoscopic laser excision surgery.[2-5] Reviews on the outcomes of radiotherapy and laser resections suggest comparable local control

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and survival with similar low risks of major complications,[6,7] although no randomized controlled trial is performed.[8] Laser resection is an effective, single use, relatively low-cost treatment which can be repeated.[9,10] Lesions that are deeper infiltrating or indistinct from non-tumourous tissue, especially those arising in the context of widespread, abnormal-appearing mucosa, seem to be more suitable for radiation therapy.[11-13]

In the last decades the treatment of advanced laryngeal carcinoma has evolved. Advanced laryngeal carcinoma was historically primarily treated by surgery (laryngectomy), but more recently the trend has shifted to (chemo)radiation. Non-surgical treatment is aimed at preservation of voice, normal respiration and swallowing and reserves surgery for salvaging purpose if needed. Two clinical studies had major effects on the management of advanced laryngeal cancer. The first in 1991, found that induction chemotherapy followed by definitive radiotherapy resulted in little difference in survival compared to patients receiving total laryngectomy and postoperative radiotherapy.[14] The second, in 2003, reported that concurrent chemotherapy and radiotherapy were superior to sequential chemoradiation or radiotherapy alone for achieving local and regional control when applied to stage III and IV laryngeal cancer with T2, T3, or "limited" T4 tumours.[15]

Standard fractionation radiotherapy (60-70 Gy at 1.8-2 Gy fraction doses) is the most commonly used modality for early stage cancer.[16] Hyperfractionation or accelerated fractionation radiotherapy have shown a higher local control rate with more acute adverse effects, as compared to standard fractionation.[17-19] Since a decade intensity-modulated radiation therapy (IMRT) has been incorporated into clinical use, a dynamic radiotherapy technique with the ability to spare vital organs, such as salivary glands, orbital tissue and the central and spinal nervous tissue.[20,21]

For advanced laryngeal carcinoma the combination of radiotherapy and chemotherapy is preferred. Concurrent chemoradiotherapy with a platinum-based chemotherapy has become the standard of care.[15] The most often used chemoradiation scheme in our centres consists of 7 weeks radiotherapy (fraction dose 2 Gy, 5x/week) combined with cisplatin (3 courses of 100 mg/m2 week 1, 4 and 7 of radiotherapy).

Although many larynges have been saved by (chemo)radiation, increasing concern arises about late toxicity and decreased survival,[22,23] which might be (partially) attributed to inappropriate patient selection for chemoradiation.[24,25] Especially patients with the most advanced stage primary laryngeal carcinoma (stage IV with cartilage invasion or involvement of the soft tissues of the neck) and expected poor tolerance of treatment seem to have better survival chances with primary laryngectomy.[25-28]

LOCAL RECURRENCES

A local recurrence is defined according to clinical criteria as the occurrence of carcinoma within three years after and localized less than two cm from the first tumour. Tumours more than 2 cm away from or after more than three years after the primary tumour are referred to as a second primary tumour.[29]

When cancer cells have remained in the patient this can be designated residual disease and outgrowth of these cells is a possible cause of local recurrent cancer. Sometimes these cells can only be detected by sensitive molecular methods and are referred to as 'minimal residual cancer'.[30] Also, fields of genetically altered cells surrounding and in the neighbourhood of the tumour can be left behind and give rise to a local recurrence, also known as 'second field tumours'.[30,31]

The local recurrence rate of laryngeal carcinoma after non-surgical treatment has been reported to be 20-46%, depending on subsite and tumour stage.[15,32-35] Surveillance is especially crucial in the first 2-3 years because two-thirds of the local recurrences and persistent or delayed lymph node metastases present in this period.[36,37] Prognosis of

patients with a recurrence depends on the time of detection, since late detection is associated with poor survival rates.[38-41]

Detection of local recurrence

The detection of recurrent laryngeal carcinoma after (chemo)radiation can be difficult. Symptoms like voice deterioration, pain, dyspnoea and dysphagia may be caused by a local recurrence, but can also be the result of post-radiotherapy changes, and are neither very sensitive nor specific.[42]

In daily clinical practice standard follow-up consists of physical examination with indirect and fiberoptic laryngoscopy, combined with imaging in selected cases. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound are the anatomic imaging modalities used for detection of recurrent laryngeal carcinoma.

The value of physical examination and anatomic imaging is sometimes limited in the detection of recurrence because of the (chemo)radiation induced changes, such as oedema, hyperaemia and fibrosis. Conventional imaging depends on soft tissue distortion and contrast enhancement and these are noted in both therapy changes and recurrent tumour. There is growing evidence that these modalities have limitations in their diagnostic accuracy.[43-48]

In general direct laryngoscopy with biopsies under general anaesthesia in case of a suspected recurrence.[42] However, it often takes several laryngoscopies to detect a recurrence: 31% of the initial laryngoscopies was false-negative (recurrence within 6 months).[42] Furthermore, trauma of multiple biopsies in heavily radiated tissue may initiate superimposed infection, chondritis, failure to heal and further oedema.[49] On the other hand, some direct laryngoscopies under general anaesthesia are performed without showing recurrence and should thus be classified as possibly preventable. In conclusion, there is room for improvement of the diagnostic work-up of these patients.

18F-FDG-PET plays an important growing role in staging, restaging, monitoring treatment and predicting prognosis in patients who have head and neck cancers.[50-54] It may be particularly useful to distinguish post-treatment changes from recurrent tumour following radiotherapy.[55] For this indication 18F-FDG-PET with or without CT has proven to be more accurate when compared with conventional imaging modalities.[46,56] Sensitivity and specificity of 18F-FDG PET for detection of residual or recurrent HNSCC were 92-94% and 82-87%, respectively, in meta-analysis.[57,58]

However, infection, inflammation, ulceration and necrosis are known post irradiation sequels associated with increased metabolic activity. As a result, PET scans can be falsely reported as tumour-positive and specificity decreases. To avoid false-positive 18F-FDG accumulation and to enable small residual disease grow to a detectable size, post(chemo)radiation evaluation of the larynx and neck should be done at least 2 months following treatment.[52,56,57,59-62] Although specificity after radiotherapy can be disappointing, sensitivity of 18F-FDG-PET is high.

Innovation in PET is focused on improving the poor quality of anatomic localization (using PET/CT and PET/MRI) and limited spatial resolution, and on the development of more specific tracers. When anatomical data is added, it may be less difficult to distinguish between metabolically active benign versus malignant tissue. In general, the combined use of 18F-FDG-PET and contrast-enhanced CT provides similar sensitivity but improved specificity and diagnostic confidence, compared with 18F-FDG-PET alone.[63,64] However, a systematic review and meta-analysis did not find a clear benefit of PET/CT over PET alone in head and neck cancer patients following (chemo)radiotherapy or as post-treatment surveillance.[57,58,65] Previous PET/CT research has focused on SUV (standardized uptake value) to differentiate between tumour and therapy-induced inflammation. There are no standardized cut-off SUVs to identify residual or recurrent disease in patients with head and neck cancer.[66]

In a systematic review, the pooled sensitivity

and specificity of 18F-FDG-PET for the detection of recurrent laryngeal carcinoma after radiotherapy were reported as 89% and 74%, respectively, with a mean prevalence rate of recurrence of 50%.[67] In a diagnostic randomized clinical trial of 150 patients with suspicion of recurrent laryngeal carcinoma after radiotherapy a conventional strategy in which all patients underwent direct laryngoscopy under general anaesthesia with taking of biopsies was compared with a 18F-FDG-PET based strategy in which patients only after positive or equivocal PET underwent direct laryngoscopy. Forty-five patients (30%) had histopathologically confirmed local disease within 6 months after randomization. The indication for direct laryngoscopy was futile in 53 out of 74 patients (72%) in the conventional strategy, compared to 22 out of 76 (29%) in the PET-based one. This difference can be interpreted as 2.3 patients to be evaluated with PET to avoid at least one unnecessary indication for direct laryngoscopy under general anaesthesia. Thirty PET scans were true-negative and 1 was false-negative. Safety of the PET-based strategy was confirmed; no adverse effects on the operability of a recurrence or surgical margins of the salvage laryngectomy in the PET-based group. This trial showed that in patients suspicious for recurrent laryngeal carcinoma after radiotherapy, PET as the first diagnostic procedure can reduce the need for direct laryngoscopy by more than 50% without jeopardizing quality of treatment.[68]

Laryngectomy as salvage

Salvage surgery, if possible, is the only therapeutic option with curative intent for proven residual or locally recurrent carcinoma after (chemo)radiation. For laryngeal carcinoma salvage surgery mostly consists of total (pharyngo-)laryngectomy which can be combined with uni- or bilateral neck dissection. In selected cases postoperative re-irradiation can be regarded. In certain cases, palliative chemotherapy may be the most appropriate therapy, with variable low response rates.

Total laryngectomy is widely recognized as one of the surgical procedures with the most impact on patients. Surgical resection compromises voice, swallowing, and the airway and may have a negative impact on the patient's quality of life. Social isolation, job loss, and depression are known sequels. The natural airway is altered by creating a permanent tracheostoma and normal vocal function is eliminated by removing the voice box. Surgical voice restoration using voice prosthesis is the optimal standard for rehabilitation in laryngectomees. The quality of voice is variable,[69] but does allow patients to reintegrate into working life.

Various types of open function preservation surgery have been described to avoid total laryngectomy. Partial laryngectomy is mainly performed to allow patients to speak without a stoma, and to minimize the risk of complications. Examples are horizontal and vertical partial laryngectomies or supracricoid laryngectomy.[16,70]

Nevertheless, for most recurrences, partial laryngectomy is no curative option and total laryngectomy will be the only operation of choice. Previous studies showed that depending on the primary tumour site most recurrences are transglottic and largely advanced (rT3-T4).[71] Also, small fields of residual tumour have been found in apparently normal areas of the laryngectomy specimen, indicating the extensiveness of recurrent disease.[43,72] Salvage partial laryngectomy seems only suitable in carefully selected patients and indications for this form of surgery vary globally.[72]

We recently performed studies on salvage laryngectomy after (chemo)radiation. In case of proven locoregional recurrence, salvage surgery is an option for a selected group of patients. Younger patients with laryngeal instead of hypopharyngeal recurrence are more often candidates for salvage surgery, probably because they have less co-morbidity and are able to undergo surgery. Salvage laryngectomy with lymph node dissection offers good oncologic and functional outcome in a selected group of patients: after radiotherapy and chemoradiotherapy 5-year local control rates of

70% and 58%, and 5-year overall survival rates of 50% and 27% were found, respectively.[73] This is in line with 5-year locoregional control rates of 70% and 5-year overall survival of 31-57% reported by other studies.[74-76] Locoregional control rate after salvage total laryngectomy for recurrent disease is dependent on the T-stage. The locoregional control rate is around 50-80% for T2,[23,77-81] 50% for T3,[77,82-84] and 20-30% for T4 tumours.[77,85] Besides surgical margins, no independent predictor for survival was found. Although patients were meticulously selected for salvage total laryngectomy, the incidence of positive surgical margins was still 10%, also in line with previous studies.[75,86-89]

Salvage surgery after radiotherapy is known to result in higher complication rates than primary surgery, with total complication rates up to 77%.[90-96] The addition of chemotherapy increases the complication risk even further.[97] Problems related to local wound healing, especially the development of pharyngocutaneous fistula, constitute the most common postoperative complication after salvage total laryngectomy.[90,98-102]

We found a total complication rate of 56% after radiotherapy and 73% after chemoradiotherapy, with fistula in 30% and 23% of the patients, respectively.[73] Other risk factors associated with fistula are: tumour subsite, T-stage, postoperative haemoglobin <12.5 g/L and positive surgical margins.[96] Bilateral PTLND was also associated with significantly more fistulae than unilateral PTLND (40% versus 22%), suggesting a need for better selection for contralateral PTLND.[103] The use of a pectoralis major flap as a protective layer between mucosa and skin reduces the risk of fistula formation.[90-104] Besides the use of pectoralis major flaps, other factors may affect the risk of fistula formation; e.g. the closure technique of the surgical defect, the start of oral intake, the use of a salivary stent and the use of antibiotics.[90-105] A salivary bypass tube is used by some clinics for circumferential fasciocutaneous reconstructions to reduce late stricture formation and may also reduce the frequency of fistula.[106] There are no uniform guidelines regarding these factors. Research focusing on the optimal peri-operative protocol, specific for salvage laryngectomy, is warranted.

Because survival rates after salvage surgery can be disappointing, and surgery is extensive with a considerable risk of complications, clear indications for the selection of patients for salvage surgery are needed to operate only on patients with reasonable survival chances and to exclude patients with irresectable disease. The same holds true for the extent of surgery. No unnecessary extensive surgery should be performed, and survival should not be compromised.

CONCLUSIONS

In case of a proven recurrence, salvage surgery will be discussed. Selection criteria for salvage surgery and its extent need to be further specified and individualized. Algorithms for salvage surgery will primarily focus on optimizing of the survival rates, and secondarily on preventing of complications. Early and reliable detection of recurrence may increase survival chances. Wound healing related problems, particularly fistula formation, are the main complications after salvage surgery. In the era of personalized medicine, future research needs to be focused on the refinement of the treatment strategy and the post-treatment diagnostic strategy for detection of recurrence, with more individualized selection criteria. Numerous patient, tumour and treatment factors need to be considered. Personalized medicine will be the future of laryngeal cancer diagnosis and treatment.

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REVIEW

Staging laparoscopy in gastric cancer

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ABSTRACT

Gastric cancer represents one of the most prevalent and deadly malignancy types globally. Although classic imaging techniques so far used for disease staging, such as computed tomography (CT), have proven efficacy in the detection of visceral metastases, their accuracy in the exclusion of peritoneal metastatic disease remains low, with a high rate of false negatives and a resultant high rate of unnecessary laparotomies, since the patients are inoperable at the time of the operation and should receive palliative chemotherapy instead. Laparoscopy, together with peritoneal cytology, suggests a recently endorsed, minimally invasive technique that achieves better sensitivity, specificity and accuracy in the staging of gastric cancer, compared with the classic imaging techniques. This review describes the technique's basic principles, compares its efficacy with that of the CT scan, mentions its main advantages and disadvantages, and suggests an algorithm for the management of patients with locally advanced gastric cancer, taking into consideration the experimental application of adjuvant Hyperthermic Intraperitoneal Chemotherapy (HIPEC).

KEY WORDS: gastric cancer, laparoscopy, cytology, staging, peritoneal metastases, HIPEC

INTRODUCTION

With about 990,000 new cases occurring every year globally,[1] gastric cancer represents the 5th most prevalent malignancy type and the 2nd in cancer mortality in the world.[2] Since gastric cancer is usually diagnosed in advanced stage, it has a poor prognosis, with high mortality/incidence ratio, while only about 50% of patients constitute candidates for curative treatment at the time of diagnosis.[3]

In patients without incurable factors, namely peritoneal disease, liver metastases and distant lymph node involvement, gastrectomy with associated lymph node dissection is the mainstay of treatment, while chemotherapy is reserved for patients with any of the above factors.[4]

While various imaging methods are utilized to achieve proper staging for gastric cancer and exclusion of incurable disease,[5,6] recent research showed that computed tomography (CT) has low sensitivity and specificity for the detection of peritoneal metastases.[7] This review focuses on the current data available, considering the usefulness of laparoscopy and peritoneal cytology as staging tools in the evaluation of peritoneal metastatic

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disease, in patients with locally advanced gastric cancer.

SURGICAL TECHNIQUE

With the patient in supine position under general anaesthesia, pneumoperitoneum, with a pressure of 10 mmHg is created and a 10 mm trocar is inserted in the umbilical region, through which a 30° optic is introduced. Two additional trocars, a 5 mm into the right upper quadrant and an 11/12 mm into the left flank, are subsequently inserted. Examination of the pelvis is facilitated by placement of the patient in the Trendelenburg position, while the upper abdomen is examined with the patient in the proclive position.[5,6]

If ascites is present, collection of fluid for cytological analysis is performed. Thorough inspection of the pelvis, hepatic surface, gastrohepatic ligament, gastrocolic ligament, right and left paracolic gutters, transverse mesocolon surface and root of mesenteric artery is performed. The gastrocolic ligament is divided for better exposure of the retrogastric space, in cases of tumours that either involve the posterior gastric wall, or situated in the proximal stomach, also facilitating inspection of the posterior surface of the stomach as well as celiac trunk lymph nodes. Both suspicious lesions of the liver and peritoneal surface, or lymph nodes, are sampled and sent for freezing histopathological examination.[8]

The procedure can be complemented with peritoneal lavage and cytological examination, if neither ascites, nor visible neoplastic implants are evident. Lavage cytology includes instillation of 300 mL of normal saline into the right and left upper quadrants and pelvis, subsequent gentle agitation of the abdomen, and collection of the washings.[9]

DISCUSSION

Gastric cancer suggests one of the most common malignancies worldwide, while it usually has a grave prognosis, due to the fact that most cases are discovered at an advanced stage, with only just above 50% constituting candidates for curative resection.[6] CT with contrast, is so far considered the standard imaging technique for preoperative assessment. Although it represents the gold-standard tool for evaluation of both the local extension, as well as the presence of distant metastases, its accuracy in the detection of peritoneal disease is low.[7] A falsely low staging of these patients, may result in an unnecessary laparotomy, increasing the intraoperative and post-operative morbidity, while delaying the initiation of either palliative or neoadjuvant chemotherapy.[6]

Staging laparoscopy has been proposed to achieve better accuracy compared with traditional imaging techniques, particularly in the detection of peritoneal metastases, therefore it has been proposed as a preoperative staging method.[6] Especially small, suspicious peritoneal nodules, including those located in the subphrenic space or Douglas pouch,[10] usually undetected by imaging techniques,[11,12] can be detected with laparoscopy, which facilitates tissue magnification, while causing minimal tissue damage.[13] Compared with state of the art CT, laparoscopy had a sensitivity of 87%, specificity of 100% and accuracy of 91%, while the corresponding values for CT were 45%, 87% and 62% respectively,[14] and similar results were reported by other studies.[15,16] In a recent review, staging laparoscopy for gastric cancer had sensitivity, specificity and accuracy of 73.7-100%, 83-100% and 93.4-100% respectively.[17]

Ever since staging laparoscopy for the assessment of gastric cancer was introduced in 1984,[18] several modifications of the technique have been implemented. Simple laparoscopy achieving a sensitivity of 89.2%, specificity of 95.8% and accuracy of 89.4% in the evaluation of the possibility of peritoneal metastases.[19] The advent of new technology in video laparoscopy, brought about an improvement of the yield of staging laparoscopy, with sensitivity, specificity and accuracy standing at 88.9%, 100% and 95.7% respectively.[20] Laparoscopic ultrasound has also been suggested as a

means of improvement of accuracy,[6,21] but studies show that it may only increase the technique's yield in the evaluation of either lymph nodes or local tumour extension, but not in the detection of peritoneal implantations.[14] The use of fluoresce with 5-aminolevulinic acid (5-ALA) has also been suggested, with promising results,[22] yet the samples are still small.[6] The tumour detection rate using 5-ALA photodynamic diagnosis has been reported to be significantly higher compared with white light,[22] but the procedure necessitates sophisticated state-of-the art equipment, like D-LIGHT System, currently not routinely available in clinical practice.[9]

Based on the findings of current literature,[23-28] positive cytology is regarded a reliable biomarker that should be taken into consideration in patients with gastric cancer, as they are potential candidates for the administration of either peri-operative or neoadjuvant chemotherapy.[23] According to large studies, approximately 4-11% of patients are expected to have a positive cytology.[29,30] Based on the prognostic role of a positive cytology, its evaluation has been endorsed by both the NCCN guidelines, as well as the AJCC staging system for gastric cancer patients.[31,32] However, there is no consensus in the treatment strategy in patients with positive cytology as the only indication of M1 disease stage.[33] In patients with positive cytology, the reported median survival times after gastrectomy has been reported to be 10.5-14.8 months,[23,24] while this figure changed to 43.2 months in cases where perioperative neoadjuvant chemotherapy was administered,[35] and adjuvant chemotherapy achieved a median survival time of 23.5 months.[36] Intraperitoneal and systemic paclitaxel combined with S-1systemic in patients with positive cytology, constitutes another promising approach under investigation.[37,38] Since Asian meta-analyses of adjuvant Hyperthermic Intraperitoneal Chemotherapy (HIPEC) after surgery for resectable high-risk gastric cancer (compared with resection only) have shown increased survival rates and decreased incidence of peritoneal recurrence,[39,40] a European study, -comprising patients with locally advanced gastric cancer, including those with positive cytology as demonstrated after the application of laparoscopy (GASTRICHIP study)-, designed to assess the benefit of adjuvant HIPEC in Western population, is ongoing.[41] Consequently, patients with positive cytology, meeting the criteria for M1 disease (Stage IV), should not undergo up-front gastric resection as a primary therapeutic intervention.[23] However, patients with excellent performance status, who are converted to cytology negative, are considered the best candidates for gastric resection.[23] Since approximately 7-16% of patients with locally advanced gastric cancer with initially negative cytology who receive neoadjuvant chemotherapy, have been shown to develop positive cytology disease, repeat of diagnostic cytology before curative resection has been suggested.[42,43]

Palliative systemic chemotherapy remains the mainstay of treatment in patients with gross peritoneal disease detected during laparoscopy.[23] However, the survival of this patient category remains poor, mainly due to the ineffectiveness of systemic chemotherapy, attributed to its inadequate diffusion into the peritoneal cavity.[44] The role of cytoreductive surgery (CRS) and HIPEC in such cases remains controversial,[45,46] with an overall median survival of 9.2 months and a 5-year survival rate of 13% reported in a study comprising 150 patients from 15 Western centres.[47] However, a randomized control trial, allocating 68 Chinese patients to CRS, with or without HIPEC -using mitomycin C and cisplatin-,[48] revealed a statistically significant improvement in overall survival duration. Recently, the comprehensive treatment for peritoneal disease in patients with gastric cancer was suggested,[49] with promising results. Its main features are the initial determination of the peritoneal cancer index by means of laparoscopy, the administration of preoperative chemotherapy, including laparoscopic hyperthermic intraperitoneal chemotherapy (LHIPEC), neoadjuvant intraperitoneal/systemic chemotherapy, HIPEC, intraoperative peritoneal lavage, CRS, as well as

early and late postoperative systemic chemotherapy.[49]

Staging laparoscopy has undergone criticism for 3 major issues. Firstly, it represents an invasive procedure, requiring general anaesthesia and pneumoperitoneum,[6,9] increasing anaesthesia time and potential related risks.[13,50] Operation-related complications though are rare, reaching up to 4.2%,[13,20,51,52] occurring at a lower rate compared with exploratory laparotomy,[10] while the in-hospital mortality in patients who underwent staging laparoscopy was significantly lower compared with that of those who underwent an exploratory laparotomy (5.3% vs. 13.1%, P< 0.05).[50] Another concern is related to its hospital cost, as it entails the use of sophisticated equipment and materials.[6,9] The technique's cost though, is compensated by the significantly longer hospitalization of patients undergoing laparotomy, relative to that of patients undergoing exploratory laparoscopy (10 days vs. 2 days, P<0.05),[50] as well as the delay in the initiation of palliative chemotherapy, owing to an unnecessary laparotomy.[6] The possibility of implantation of tumour cells at puncture sites of the trocars, owing to tumour dissemination caused by the induced pneumoperitoneum, constitutes the third issue to be taken into consideration.[6] However, several studies have put this theory into question, since it has been reported that the incidence of metastatic dissemination at trocar sites, does not differ significantly from that described in cases of local tumour recurrence at the site of the incision, in cases of laparotomy performed for treatment of gastrointestinal tumors.[53] These findings reveal that tumour implantation, either at trocar sites or at the laparotomy incision, should be attributed to the biological behaviour of the tumour cells, rather than to the pneumoperitoneum or the surgical handling.[6]

Consequently, it is widely accepted that only a subgroup of patients with gastric cancer benefit from staging laparoscopy and cytology.[6,23] No indication is evident in patients with bleeding, perforation, or stenosis, since they will require some type of intervention.[6,23] The same applies for patients with early stage disease, who have a high probability of a curative surgical operation.[6,23] Therefore, staging laparoscopy should be reserved for patients with locally advanced disease (T3 and T4 tumours), most commonly associated with peritoneal disease.[13] While peritoneal metastases in stage II disease are detected with a probability of 50% using classic imaging techniques, in stage III disease, peritoneal metastases might be missed in 57-98% of cases.[55] As previously reported, CA-125, tumour size>4 cm, Borrmann type III/IV, invasion of serosa, and lymph node metastases, have been positively and significantly correlated with peritoneal metastases and/or positive cytology,[20,55,56] suggesting risk factors,[9] and staging laparoscopy is indicated, especially in those patients with 2 or 3 of these risk factors.[9] An additional benefit for patients with locally advanced tumours suspicious of invading adjacent structures, or for those in whom lymph nodes are found too close or adherent to the celiac trunk by CT, is the assessment of regional tumour extension and examination of the area of the celiac trunk respectively.[6,9] Both of these situations would necessitate neoadjuvant treatment administration to increase R0 resection rate.[6,9] Likewise, patients with a proven early gastric cancer using endoscopic ultrasound (T1, T2, N0), can abstain from cytology evaluation, since its yield is extremely low in the above patient subcategory (about 4%), while it is approximately 25% in high risk patients (T3/T4, N+).[29] Based on the available data, the proposed algorithm for the management of patients with locally advanced gastric cancer is depicted in figure 1, although further studies are required to establish the standard of care for patients with positive cytology.

In conclusion, laparoscopy for staging of gastric cancer, with the concurrent utilization of peritoneal fluid cytology, represents a useful and accurate method for the detection of occult peritoneal metastatic disease. It seems that it can improve treatment decision-making in patients with locally advanced gastric cancer, and decrease the rate of

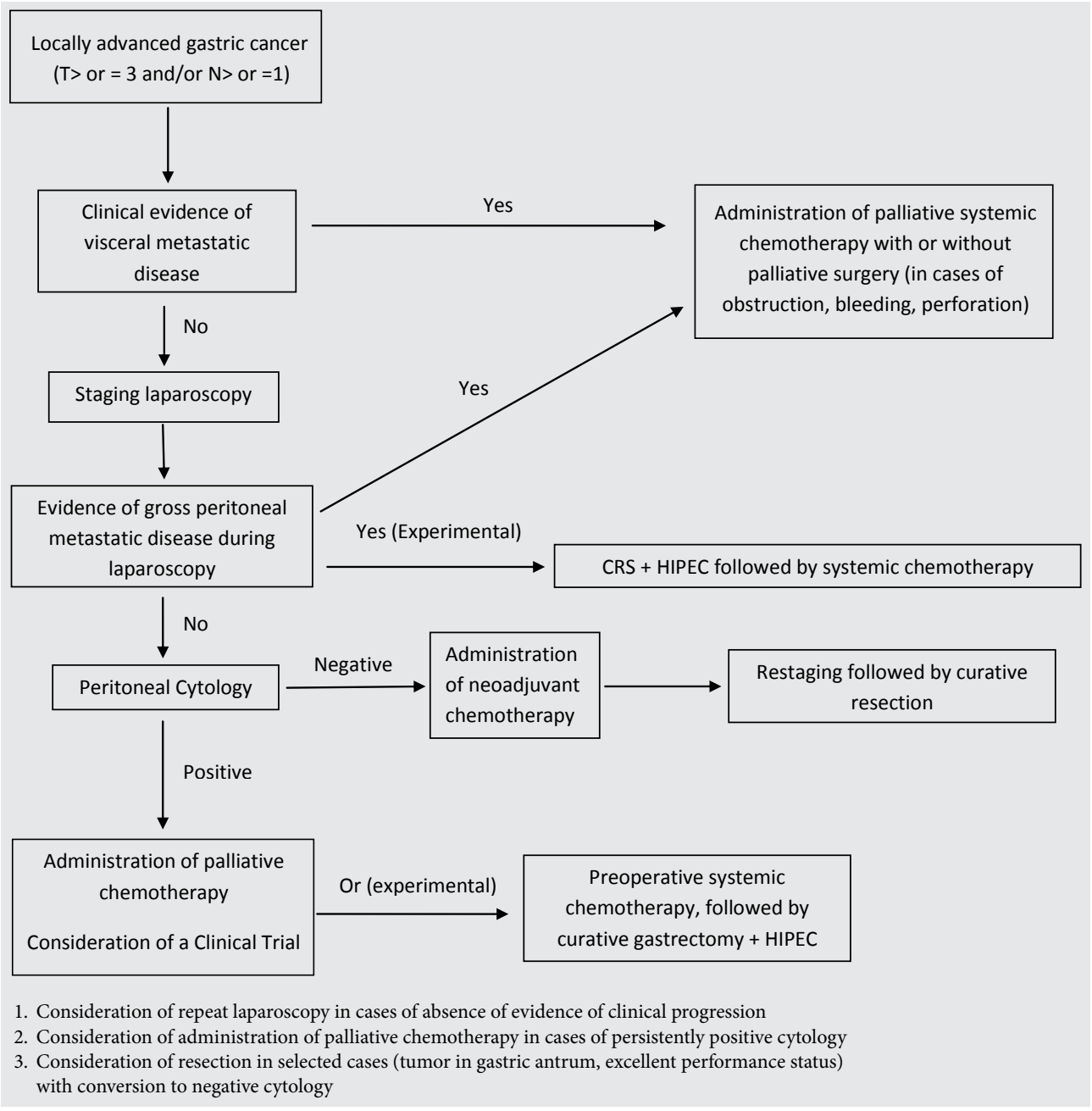

Figure 1. Proposed algorithm of management for patients with locally advanced gastric cancer. CRS: Cytoreductive Surgery, HIPEC: Hyperthermic Intraperitoneal Chemotherapy.

unnecessary exploratory laparotomies. However more studies are required to provide and determine the best treatment option for patients with positive cytology as the only evidence of M1 disease.

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REVIEW

Treatment of acute malignant colorectal obstruction: diverting colostomy as a bridge for elective surgery is a safe and valid alternative

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ABSTRACT

Acute bowel obstruction by colon cancer occurs relatively frequently and requires immediate intervention. The optimal curative approach for obstructing colorectal carcinoma remains a topic of discussion. Primary resection with anastomosis is associated with an increased risk of anastomotic leakage, while primary resection with an intentionally temporary colostomy may lead to a difficult second procedure or an increased risk of permanent colostomy. Further, the patient may be in a poor condition to undergo primary resection. Primary decompression of the bowel with a colostomy or stent and delayed colectomy has the advantage of providing time for improvement of the patient's condition, recovery of the initially dilated large bowel, accurate disease staging and planning of eventual preoperative therapy. Further, in the absence of dilated bowel the surgical procedure may be performed laparoscopically. Since placement of a self-expanding metallic stent as a bridge to elective surgery is associated with a high complication rate and probably with impaired oncological outcome, it should be only considered as an alternative to emergency surgery in those who have an increased surgical risk or as a palliative procedure. Creation of diverting colostomy as a bridge to elective surgery is a safe and valid alternative. Although a second operation is required, the total morbidity and mortality are not higher than for primary resection, while the rate of a permanent colostomy is significantly lower. Moreover, there are indications that this approach is associated with better oncological outcome.

KEY WORDS: colorectal cancer, bowel obstruction, primary resection, diverting colostomy, self-expanding metallic stent

INTRODUCTION

Approximately 20% of the patients with colorectal cancer present with acute bowel obstruction.[1,2] Individuals with obstructed carcinoma of the colon have a higher operative mortality and morbidity and a shorter long-term survival. The higher operative mortality and morbidity

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may depend entirely on the choice of operative procedures.[3] The optimal treatment for those patients has been a topic of controversy. Ideally, the curative treatment of patients with colorectal cancer with acute obstruction would be the same as that of colorectal cancer patients who do not require emergency surgery. However, this standard treatment might not be feasible in those patients due to several risk factors.[4] Most of the patients have a poor general health status, an impaired nutritional status and an advanced disease status, whereas these conditions and the dilated wall of the proximal bowel render the anastomosis prone to leakage. All these parameters are associated with increased morbidity and mortality. On the other hand, an immediate solution for the bowel obstruction is required. Therefore, staged procedures may be indicated, in which case the primary operation is shorter, less extensive and more tolerable by the deteriorated patients and high-risk anastomosis can be avoided, instead of primary resection. Disadvantage of such an approach is that the subsequent intended resection of the tumour requires a second surgical procedure and the cumulative morbidity and mortality of both surgical procedures may be higher than that of primary resection and anastomosis. Another issue is that, when the bowel resection is postponed, the tumour remains in place and oncological treatment is delayed.

While for curative uncomplicated right colon cancer (i.e. located proximal to the splenic flexure) primary colectomy and ileocolic anastomosis is the standard of care, in the case of acute obstruction, alternative surgical procedures include: 1) colectomy with enterostomy with secondary anastomosis, 2) decompression enterostomy and secondary colectomy with anastomosis when the deteriorated condition of the patient and his bowel are improved and 3) by pass bowel anastomosis. In case of left bowel obstruction (i.e. located distal to the splenic flexure) in curative colon cancer, alternative approaches for primary left colectomy and colocolonic or colorectal anastomosis are: 1) colectomy with colostomy and secondary colocolonic or colorectal anastomosis (i.e. Hartmann procedure), 2) colostomy and secondary bowel resection with anastomosis, 3) subtotal colectomy with ileocolonic or ileorectal anastomosis, avoiding anastomosis with dilated proximal colon but causing increased diarrhoeic bowel movements and 4) initial management of the obstruction by endoscopic placement of an expanding stent as a bridge to surgery. In the case of acute obstruction by a rectal carcinoma a diverting colostomy may be initially required instead of a low anterior rectosigmoid resection or an abdominoperineal resection.

The decision on which procedure is best to be performed in a certain case may be difficult and is mostly based on the surgeon's individual opinion and preference. The aim of this review is to seek for scientific evidence in the literature regarding the optimal treatment in the case of acute bowel obstruction in colorectal cancer patients.

PRIMARY RESECTION AND ANASTOMOSIS

In a retrospective series of 243 emergency operative procedures for obstructing lesions in colorectal cancer patients,[5] the primary resection rate was 92%. Totally, 81% of the patients underwent primary resection and concurrent bowel anastomosis, in 90% of the patients with right-sided colon cancer and in 74% of the patients with an obstructing tumour of the left colon. Among the 101 primary anastomoses in patients with left-sided obstruction, segmental resection with on-table lavage was performed in 75 patients and subtotal colectomy was performed in 26. The overall operative mortality rate was 9.4%, while that of the patients with primary resection and anastomosis was 8.1%. The anastomotic leakage rate for those with primary resection and anastomosis was 6.1%. There were no differences in the mortality or leakage rates between patients with right-sided and left-sided lesions (mortality:

7.3% versus 8.9%, p=0.79; leakage: 5.2% versus 6.9%, p=0.77). Colocolonic anastomosis did not show a significant difference in leakage rate when compared with ileocolonic anastomosis (6.1% versus 6.0%, p=1.0). From these retrospective data it appears that after proper patient selection for both left-sided and right-sided obstruction primary resection and anastomosis is not associated with increased mortality, whereas the leakage rate is acceptable. The authors conclude that the single-stage procedure should be the objective for the treatment of patients with obstructing colorectal cancers, except when patients are haemodynamically unstable during surgery or when the condition of the bowel is not optimal for primary anastomosis.

COLOSTOMY OR STENT AS BRIDGE TO ELECTIVE SURGERY

However, in patients with acute malignant bowel obstruction who are in bad general condition or have a dilated proximal bowel, a decompression of the bowel by a diverting colostomy or a stent may serve as a bridge to elective surgery. These procedures are mainly indicated for left sided colonic (i.e. distal to the splenic flexure) or rectal obstruction, since primary right colectomy with anastomosis of the ileum with non-dilated colon is so not prone to anastomotic leakage. In case of synchronous metastatic disease, creating a diverting stoma or placing a self-expandable metallic stent, may be the definite palliative surgical treatment before starting systemic chemotherapy. The systemic chemotherapy may help to select patients for bowel resection and metastasectomy.

In case of potentially curative disease, the advantages of performing a colostomy or placing a self-expandable metallic stent is the immediate solution for the bowel obstruction and providing in this way time for improvement of the patient's condition, recovery of the initially dilated large bowel, accurate disease staging and, especially in case of rectal cancer, planning of eventual preoperative therapy. Further, in absence of dilated bowel the surgical procedure may be performed laparoscopically. Finally, having a better optical surgical field without dilated bowel and the patient's condition allowing for a longer duration of the operation, the procedure may possibly be performed in an oncologically more accurate way. Disadvantages of this staged procedure are the need for a second intervention and the possibility of a higher accumulative morbidity.

Placement of a stent as a bridge to elective surgery versus primary colectomy

The use of a self-expandable metallic stent as a bridge to surgery when compared with emergency colectomy for acute obstruction of the left colon or the rectum appeared to be safe and resulted in improved short-term outcome in recent meta-analyses.[6,7] The colonic stent group achieved significantly more favourable rates of permanent stoma, primary anastomosis, wound infection, and overall complications, while there was no significant difference between the two groups in anastomotic leakage, mortality, or intra-abdominal infection. However, two recent multicenter randomized trials were prematurely closed due to high complication rates, especially technical failure and bowel perforations, requiring emergency surgical intervention.[8,9] Stent-related bowel perforations are more frequently seen in total obstruction and a length of stricture longer than 4 cm.[10-12] Moreover, there is concern about impaired oncological outcome after placement of a stent. In one of the recent multicenter trials, the recurrence rate was higher in the stent group (4-year disease-free survival 30% vs. 49%), especially in the subgroup with guidewire-or stent-related bowel perforation (4-year disease-free survival 0%, p=0.007).[13] Further, a French retrospective comparative study, using a propensity score analysis to correct for selection bias, reported significant lower survival rates for stenting when compared with emergency surgical intervention (21% vs. 48%, respectively (P=0.02).[14] In a Danish nation-

wide cohort study,[15] a trend for an increase of the 5-year recurrence risk was observed after stenting instead of emergency surgery for acute left-sided colon obstruction (49% vs. 40%, hazard ratio 1.12, 95% confidence interval 0.99-1.28). In another comparative study,[16] a significant higher local recurrence rate was observed after stenting (32% vs. 8%, p=0.038), without however a significant difference in overall survival. This potentially negative impact on oncological outcome may be explained by spread of cancer cells by tumour manipulation, bowel dilatation and bowel or tumour perforation during its placement as well as ulceration of the tumour and the peritumoral tissues by the stent.[9,16]

Based on the available evidence, the European Society of Gastrointestinal Endoscopy provided clinical guidelines for the use of self-expandable metallic stents for obstructing colorectal cancer,[10,17] wherein its use "as a bridge to elective surgery is not recommended as a standard treatment of symptomatic left-sided malignant colonic obstruction (strong recommendation, high quality evidence)". According of these guidelines, "for patients with potentially curable obstructing left-sided colon cancer, stent placement as a bridge to elective surgery may be considered as an alternative to emergency surgery in those who have an increased surgical risk, i.e. age above 70 years and/or ASA class ≥III (weak recommendation, low quality evidence)". Further, stent placement is recommended as the palliative treatment for patients with malignant colonic obstruction, unless the patient is simultaneously being treated with angiogenesis inhibitors (e.g. bevacizumab) as they increase the risk of stent perforation.

Regarding stent placement for acute malignant obstruction of the right colon available data are sparser. In a recent meta-analysis of cohort studies,[18] primary resection in 2873 patients seemed to be associated with higher mortality and major morbidity rates than stent placement and elective resection in 155 patients (11% vs. 0%, p=0.009 and 24% vs. 1%, p=0.049, respectively). In addition, stent placement resulted in fewer anastomotic leakages and permanent ileostomies. However, as no high-level studies are available on the optimal treatment of right-sided colon obstruction and proximal stenting is considered technically challenging, future comparative studies are warranted for the development of an evidence-based clinical decision guideline.

Diverting colostomy and delayed colectomy versus primary colectomy

Another choice for postponing definite resection of the large bowel obstruction and providing the opportunity for elective surgery is the creation of a diverting colostomy, or much less frequent, an ileostomy. Unfortunately, the data available to support either approach are relatively sparse. In most studies, the number of included patients is limited, while only one randomized trial is available. In a meta-analysis of eight comparative studies (among which one randomized trial),[19] including 2424 patients with acute malignant left-sided colonic obstruction, the morbidity and mortality rates were not significantly different. However, for patients with initially constructed colostomy, the proportion of creation of a primary anastomosis at the time of resection of the obstructed bowel was significantly higher (51% vs. 11%, p<0.00001) and the risk of permanent colostomy significantly lower (22% vs. 6%, p<0.001) than for patients who underwent emergency colectomy. Only in two studies the anastomotic leakage rate was reported. In one study there was no significant difference in anastomotic leakage,[20] whereas in the second study anastomotic leakage was observed more frequently after primary resection.[21] While in the older studies the cumulative hospital stay was higher in the group of patients undergoing colostomy and secondary resection of left-sided obstructive colon cancer, in a recent large prospective Dutch national registry the total hospital stay was shorter for the colostomy and delayed resection group when compared with the emergency colectomy group (12 versus 16 days).[22]

This may be attributed to the increasing use of the laparoscopic approach in elective surgery for colon cancer, which is usually not feasible in the emergency setting due to dilated bowel.

It is of major importance to choose the site of the emergency diverting colostomy correctly, especially in rectal cancer. In a recent study,[23] it appeared that approximately one third of the diverting colostomies were considered to be placed inappropriately in patients with rectal cancer. In case of a low anterior resection as definite treatment, a right-sided diverting transverse double loop colostomy is indicated, while for a subsequent abdomino-perineal resection, an end sigmoid colostomy is advocated. Stoma placement on the left upper abdomen should be avoided since it could compromise the descending colon in case of a low anterior resection and anastomosis.

The data for right-sided obstructive colon cancer are even sparser. In an analysis of patients with acute obstruction of proximal colon cancer registered in the Dutch Surgical Colorectal Audit,[24] 95% of the 1860 patients underwent acute resection, while the remaining patients were treated by initial decompression with stoma construction or stent placement followed by secondary resection. Because a significantly lower postoperative mortality rate was seen in the group of patients initially treated with a stent or stoma (8.8% vs. 2.4%, p=0.04), also in case of acute malignant obstruction of the right colon, a bridging strategy may be a valid alternative.

From the above data it seems that diverting colostomy as a bridge to surgery is a safe and valid alternative for primary resection, but what are the data regarding oncological outcome? Again there are not many studies on this issue available. In the only randomized trial,[25] 36 patients underwent diverting colostomy and delayed resection of the tumour, while 50 patients underwent immediate colon resection for acute obstruction of left-sided colon cancer from 1978 to 1993. Local and overall recurrence rates were similar, but the median disease-free duration was significantly higher in the group with staged resection (18 versus 12 months, p=0.02). In two retrospective comparative studies,[2,26] there was no difference in survival, while in two other studies[27,28] survival was better after primary emergency resection than after diverting colostomy and delayed resection for obstructive colorectal cancer. However, in a recent comparative study,[21] the survival tended to be longer in patients with diverting colostomy and delayed resection of obstructing left-sided colon cancer (median survival 105 vs. 66 months, p=0.088). In this study, although delayed resection was more frequently performed in obstructing rectal cancer (28% vs. 11%, p=0.021), the local recurrence rate tended to be higher in the group of patients with primary resection for their obstructing colorectal cancer (10.2% vs. 5.6%, p=0.326). Most importantly, the number of lymph nodes harvested were significantly higher after diverting colostomy and delayed resection than after primary resection in patients with obstructing rectal carcinoma (14.6 vs. 7.2, p=0.002), while there was no difference in case of more proximal left-sided colon cancer. One may speculate that the extent of tumour excision and lymph node dissection would have been limited in the face of dilated bowel filled with a large amount of faecal material, with delayed resection facilitating meticulous dissection which is most important in rectal cancer surgery. Difference in survival might be the result of the invasive potential of tumour cells, which might be enhanced by the oedematous conditions of the bowel and more manipulation of the tumour by the surgeons. Both instances may facilitate spreading the tumour cells into the lymphatic vessels and vasculature to cause recurrence. In case of locally advanced rectal cancer, diverting colostomy may give patients the chance to undergo neoadjuvant chemoradiotherapy before tumour resection.

CONCLUSIONS

As potentially curative treatment for acute obstruction of colon carcinoma resection with

primary anastomosis is usually safe, except when the patient or the proximal colon is in poor condition. Primary colectomy with an intentionally performed temporary colostomy (Hartmann procedure) is an alternative in the latter patients, but the subsequent operation to restore the bowel continuity may be difficult and often the patients remain with a permanent colostomy. Primary decompression of the bowel with a colostomy or stent and delayed colectomy has the advantage of providing time for improvement of the patient's condition, recovery of the initially dilated large bowel, accurate disease staging and planning of eventual preoperative therapy. Further, in absence of dilated bowel the surgical procedure may be performed laparoscopically. Finally, having a better optical surgical field without dilated bowel and the patient's condition allowing for a longer duration of the operation, the procedure may possibly be performed in an oncologically more accurate way. Since stent placement as a bridge to elective surgery is associated with a high complication rate and probably with impaired oncological outcome, it should be only considered as an alternative to emergency surgery in those who have an increased surgical risk, i.e. age above 70 years and/or ASA class ≥III, or as a palliative procedure. Creation of diverting colostomy as a bridge to elective surgery is a safe and valid alternative. Although a second operation is required, the total morbidity and mortality are not higher than for primary resection, while the rate of permanent colostomy is significantly lower. Moreover, there are indications that this staged approach is associated with better oncological outcome.

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CASE REPORT

Individualized treatment for an eccrine porocarcinoma of the scalp using lymphoscintigraphy*

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ABSTRACT

This case report describes a patient with an eccrine porocarcinoma of the scalp and shows the implication of lymphoscintigraphy for the extent of lymph node dissection in a non-melanoma skin cancer patient with already known ipsilateral lymph node metastases.

KEY WORDS: eccrine porocarcinoma, non-melanoma skin cancer, lymph node metastasis, lymphoscintigraphy, sentinel node

CASE REPORT

A 46-year-old woman presented with (cytologically proven) lymph node metastases on the right side of the neck (retroauricular, parotid gland and neck) of a previously excised eccrine porocarcinoma of the scalp, located on the paramedian right side of the coronal line.

Two years ago the primary tumour was supposed to be a basal cell carcinoma and was treated with Mohs surgery. There was no clinical evidence of local recurrence at the time of the lymph node metastases. An FDG-PET/CT was performed and showed besides the already known ipsilateral lymph nodes metastases no evidence for local recurrence, contralateral lymph node metastases or distant metastases.

To identify potential contralateral drainage and detect eventually non-FDG-PET/CT avid micrometastases the sentinel lymph node biopsy procedure was used. In 4 quadrants around the scar of the primary lesion (Figure 1) injections of 99mTechnetium (^{99m}Tc)-labeled nanocolloidal albumin were given. Directly following the injections drainage was visualized by using planar lymphoscintigraphy. A sentinel lymph node (the directly draining lymph node) was identified on

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Figure 1. Scar of the former excision of the eccrine porocarcinoma of the scalp, paramedian right at the coronal line.

the right side, but not on the left side of the neck (Figure 2 and 3). It was decided that no left sided lymphatic drainage existed of the original tumour site. Because of the already demonstrated ipsilateral lymph nodes metastases treatment of the right neck was planned instead of only harvesting the sentinel nodes. Therefore a superficial parotidectomy and posterolateral neck dissection was performed on the right side of the neck. The left side remained untreated. Histopathological analysis of the dissection specimen showed 9 lymph nodes containing metastasis of the eccrine porocarcinoma, in 2 of them extra capsular spread was present. Patient received postoperative radiotherapy to the region of the parotid gland and neck on the right side to a total dose of 66 Gray in 33 fractions (regular

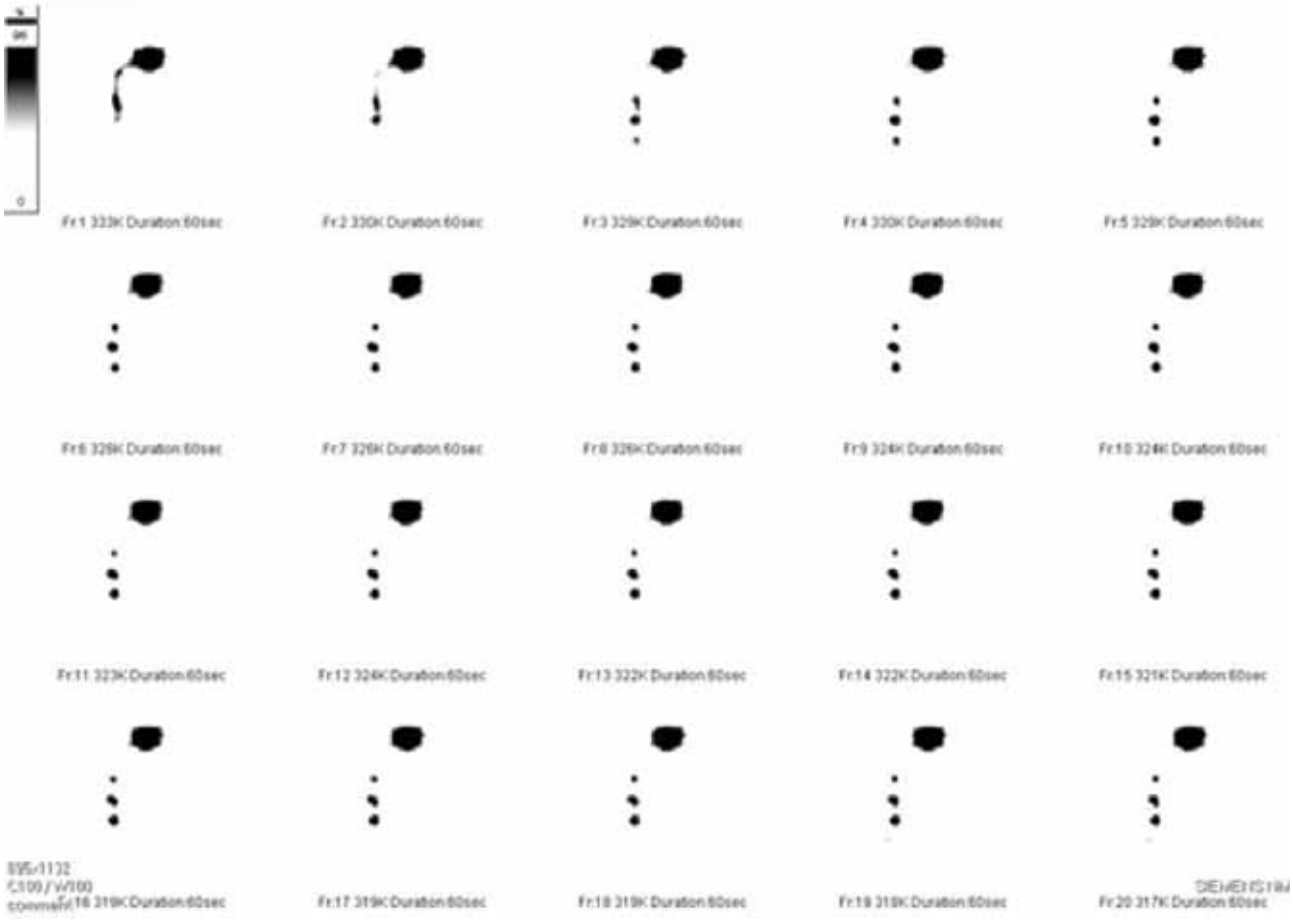

Figure 2. Dynamic planar lymphoscintigraphy after injections of ^{99m}Tc-labeled nanocolloidal albumin around the scar of the primary lesion. A sentinel lymph node (cranial hotspot) and 2 second echelon nodes (more caudal hotspots) on the right side could be identified, but no drainage to the contralateral side.

Figure 3. Marks on the skin of the sentinel lymph node and 2 second echelon nodes (purple).

schedule for mucosal head and neck squamous cell carcinoma and melanoma). Until now, currently 8 years after this treatment, no evidence of local or regional disease is present. However, lung metastases were unfortunately diagnosed 4 years after treatment. After a period of watchful waiting she received stereotactic radiotherapy (5 fractions of 11 Gray) due to progression of the 2 lung metastases. During follow-up both lesions remained in regression and no new lesions were observed.

DISCUSSION

Eccrine porocarcinoma

Eccrine porocarcinoma is a rare type of skin cancer arising from sweat glands. Porocarcinoma counts for approximately 17% of all malignant adnexal tumours and may arise as transformation of long standing benign poroma or *de novo*. Malignant transformation may be associated with spontaneous bleeding, ulceration, itching, pain and abrupt growth. An eccrine poroma is more common and mainly located at the lower extremity, occasionally at the upper extremity (palm of the hand), but rarely at the head and neck region. Eccrine porocarcinoma presents particularly in the middle-aged and elderly population, with no racial predilection and equally in men and woman. Approximately 60% of the eccrine porocarcinomas are situated on the lower extremity. Typical clinical presentation is a solid, asymptomatic erythemous, or purple, nodule smaller than 2 centimeters.[1] Lymph node metastases occur in 20% of the patients.[2] In literature so far, only 39 cases with eccrine porocarcinoma of head and neck region are reported.[3-15]

The treatment of choice is a surgical excision. Standard local wide excision but also Mohs microscopic surgery is reported for eccrine porocarcinoma. The use of radiotherapy as first treatment seems limited. FDG-PET/CT is able to detect metastases of the eccrine porocarcinoma.[16] Fine needle aspiration cytology could be helpful to prove the metastatic deposits. Chemotherapy is used to treat distant metastases with limited response.[1]

Lymphoscintigraphy

To predict the metastatic spread of tumours some models are used, mainly based on histopathological findings of the lymph node dissection specimens. O'Brien et al.[17] developed a predictive model for head and neck melanoma of the skin. Their model predict for melanoma in the coronal line (an area of 5 centimetres from ear to ear) a lymph drainage pattern to levels I to V in the neck and to the parotid gland.[17] By using lymphoscintigraphy after peritumoural injections of ^{99m}Tc-labeled nanocolloidal albumin the specific lymph drainage pattern of each individual tumour in the complex head and neck region can be visualized.

With lymphoscintigraphy the drainage pattern appears discordant to this model in 23-34% of the cases, particularly due to drainage towards retroauricular lymph nodes.[18,19] To identify individual drainage patterns with lymphoscintigraphy, determining the extent of the lymph node dissection, further research for these melanomas is desirable. This results in more personalized treatment associated with less overtreatment (prevention of unnecessary elective and extended neck dissections) and less undertreatment (no treatment of occult lymph node metastases).

In oral cavity cancer sentinel lymph node biopsy is used to stage the clinically negative neck, but the procedure could also be helpful in case of a positive ipsilateral neck side by evaluating the contralateral neck side. Especially in tumours close to (or crossing) the midline the procedure can be supportive in the decision to perform a uni- or bilateral neck dissection.[20]

Application of the sentinel lymph node biopsy for an eccrine porocarcinoma is reported only 12 times. In most cases the sentinel lymph nodes were negative. Norie et al[21] reported 6 patients with an eccrine porocarcinoma and all of them had negative sentinel lymph node biopsies. Shiohara et al[22] reported 2 patients with an eccrine porocarcinoma and a sentinel lymph node biopsy, of which 1 patient had an occult lymph node metastasis. Stoffels et al,[23] Sahn and Lang,[24] Sheff and Macdougall[25] and Motomura and Ishii [26] reported all 1 patient with an eccrine porocarcinoma and a negative sentinel lymph node biopsy.

Considerations

Our patient had an eccrine porocarcinoma of the scalp, paramedian right at the coronal line. The ipsilateral sentinel lymph node could be well visualized, however due to the proven lymph node metastases on this neck side there were no therapeutical consequences for sentinel node biopsy in the ipsilateral neck. The sentinel lymph node was not separately taken from the lymph node dissection specimen for histopathological analysis. The ipsilateral drainage pattern was in reasonable agreement as expected in literature.[27]

If lymphoscintigraphy will be performed after wide local excision, it could be possible to visualize a more broad lymph drainage pattern (even to the contralateral side) compared with direct peritumoural injections. The lymphoscintigraphy of our patient shows no contralateral drainage, resulting in a wait and see follow-up instead of an elective neck dissection. The long-term follow-up justified that treatment, reducing reasonably the morbidity of the treatment.

CONCLUSION

Lymphoscintigraphy could be valuable for other types of malignant skin cancers than melanoma, for example for eccrine porocarcinoma, and could be used to identify (or exclude) contralateral lymph node metastases.

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Book Review

Ένα υπέροχο ταξίδι στην ιστορία και εξέλιξη της ανατομικής

E. de Bree

Κλινική Χειρουργικής Ογκολογίας, Πανεπιστημιακό Νοσοκομείο Ηρακλείου

***«Ιστορικά στοιχεία και άλλα παραλειπόμενα της εξέλιξης της ανατομικής»*, Γεώργιος Νικ. Σχορετσανίτης**

Εκδότης: BHTA medical arts
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Η Ανατομία δεν είναι μόνο το βιβλίο Gray's Anatomy ή το βιβλίο Surgical Anatomy του Σκανδαλάκη αλλά μια επιστήμη που πέρασε πολλές δυσκολίες και δοκιμασίες παγκοσμίως.

Ο συνάδερφος χειρουργός Γεώργιος Σχορετσανίτης καταγράφει στο βιβλίο του «**Ιστορικά στοιχεία και άλλα παραλειπόμενα της εξέλιξης της ανατομικής**» λεπτομερώς και με ελκυστικό και πετυχημένο τρόπο την ιστορική διαδρομή και εξέλιξη της ανατομικής. Σε αυτό το υπέροχο ταξίδι δεν αναφέρεται μόνο στα ευρύτερα γνωστά, αλλά και στα -για τους περισσότερους από εμάς- άγνωστα ιστορικά στοιχεία της ανατομικής από διάφορες χώρες του κόσμου. Ο ίδιος ο συγγραφέας, συνοψίζοντας το περιεχόμενο του βιβλίου του:

«*Η Ανατομία, ένας από τους ακρογωνιαίους λίθους της μακράς και επίπονης διαδικασίας της εκπαίδευσης του γιατρού, έχει υπέροχη ιστορία και θεωρείται η βάση των βιολογικών επιστημών. Οι επιστημονικές μέθοδοι έχουν βελτιωθεί δραματικά όλους αυτούς τους αιώνες, από την εξέταση των ζώων μέχρι την ανατομή των πτωμάτων, χρησιμοποιώντας πολύπλοκες τεχνικές που αναπτύχθηκαν κυρίως τον 20ό αιώνα. Η εκπαίδευση της ανατομίας εξελίχθηκε παράλληλα σε όχημα και για την ηθική διαπαιδαγώγηση των*

φοιτητών. Η ιστορία έχει καταγράψει απίθανες και αναρίθμητες πηγές από τις οποίες προέρχονταν τα πτώματα. Ανάμεσά τους ήταν σώματα εκτελεσθέντων, πτώματα που εκλάπησαν από τα νεκροταφεία, αζήτητα πτώματα φτωχών και φυλακισμένων που κατέληξαν για διαφόρους λόγους στα νοσοκομεία, τα πτωχοκομεία και στις φυλακές, πτώματα ατόμων που αυτοκτόνησαν ή έπεσαν θύματα μονομαχίας, καθώς και ατόμων που δολοφονήθηκαν αποκλειστικώς για σκοπούς εκπαίδευσης. Η σύγχρονη ανατομική, αρκετά ευαίσθητη σε θέματα αξιοπρέπειας του ανθρωπίνου σώματος, ως επί το πλείστον χρησιμοποιεί σώματα που προέρχονται από δωρεές, ενώ σε πολλές χώρες, η χρήση των αζήτητων πτωμάτων είναι νόμιμη.

Το βιβλίο ετούτο ταξιδεύει τον αναγνώστη σε όλο αυτό το υπέροχο ταξίδι και στα μικρότερα μυστικά του, αυτά που δεν έγιναν τόσο γνωστά όσο έπρεπε, για διαφόρους λόγους!»

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