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Editorial office
Radiology and Oncology
Institute of Oncology
Zaloška 2
SI-1000 Ljubljana
Slovenia
Phone: +386 1 5879 369
Phone/Fax: +386 1 5879 434
E-mail: gsersa@onko-i.si

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CONTENTS

Radiology and Oncology is covered in *Biomedicina Slovenica, Chemical Abstracts, EMBASE / Excerpta Medica, Sci Base and Scopus*

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case report

Mediastinitis and bilateral pleural empyema caused by an odontogenic infection

Mirna Juretic[1], Margita Belusic-Gobic[1], Melita Kukuljan[3], Robert Cerovic[1], Vesna Golubovic[2], David Gobic[4]

[1]Clinic for Oral and Maxillofacial Surgery, [2]Clinic for Anaesthesiology and Reanimatology, [3]Department of Radiology, [4]Clinic for Internal Medicine, Clinical hospital, Rijeka, Croatia

Background. *Although odontogenic infections are relatively frequent in the general population, intrathoracic dissemination is a rare complication. Acute purulent mediastinitis, known as descending necrotizing mediastinitis (DNM), causes high mortality rate, even up to 40%, despite high efficacy of antibiotic therapy and surgical interventions. In rare cases, unilateral or bilateral pleural empyema develops as a complication of DNM.*

Case report. *This case report presents the treatment of a young, previously healthy patient with mediastinitis and bilateral pleural empyema caused by an odontogenic infection. After a neck and pharynx re-incision, and as CT confirmed propagation of the abscess to the thorax, thoracotomy was performed followed by CT-controlled thoracic drainage with continued antibiotic therapy. The patient was cured, although the recognition of these complications was relatively delayed.*

Conclusions. *Early diagnosis of DNM can save the patient, so if this severe complication is suspected, thoracic CT should be performed.*

Key words: mediastinitis; empyema, pleural; periapical abscess – complications

Introduction

Acute suppurative mediastinitis is a life-threatening infection infrequently occurring as a result of the propagation of odontogenic infection, and is described as descending necrotizing mediastinitis (DNM). Pleural empyema is reported as a rare complication of acute mediastinitis.[1-6] Clinical manifestations of mediastinitis are frequently nonspecific. If the diagnosis of mediastinitis is suspected, thoracic CT is required regardless of negative chest X-ray. In the treatment of advanced mediastinitis, administration of antibiotic therapy alone is ineffective unless aggressive surgical interventions including wide incisions, debridement, excision of necrotic tissue and drainage of all abscessed regions are included.

A case of a young patient with mediastinitis and bilateral pleural empyema caused by odontogenic infection is presented.

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Correspondence to: Belusic-Gobic Margita, MD, KBC Rijeka, Department of Oral and Maxillofacial Surgery, Tome Strižića 3, 51 000 Rijeka, Croatia; Phone/Fax: +385 51218279; E-mail: mfk@kbc-rijeka.hr

Case report

A previously healthy 23-year-old man presented to his dentist complaining of toothache in the region of the right mandibular third molar. Root trepanation was performed and antibiotic therapy (amoxicillin) was initiated but the patient's condition worsened with severe pain and marked swelling. On the 9th day after the occurrence of toothache, the patient was referred to the Clinic of maxillofacial and oral surgery. Physical examination revealed trismus, a firm swelling in the right submandibular and in a portion of supramandibular regions, oedema and erythema of retromolar mucosa. Due to an extensive dental caries the crown of the tooth was completely destroyed. The patient was subfebrile to 37.5 ^{0}C, had dysphagia and slightly muffled voice. On admission to hospital, initial preoperative procedures were performed. Laboratory tests showed signs of inflammation: (WBC 12.6 x 10^9/ L, fibrinogen 9.09 g/l, CRP 18.9 mg/dL). Chest X-ray revealed no irregularities. The same evening under general endotracheal anaesthesia external incision was done by opening the submandibular triangle to the mandibular periost and to the buccal region, where purulent content was found to be less than expected. A larger amount of pus was obtained by a wide incision in the retromolar space. Ciprofloxacin 400 mg/12 h i.v. and metronidazole 500 mg/8 h were prescribed till the results of cultures were obtained. On the 1st postoperative day the patient's condition improved subjectively, but he continued to be subfebrile, had dysphagia accompanied by sore throat and suppurative spit. Due to his private problems, he insisted on being discharged that same day. Four days later, the patient returned with worsened general condition and local findings. He complained of severe buccal and retromolar pressure, had severe dysphagia and a muffled voice («hot potato voice»), productive cough, and temperature of 37.8^{0}C. Clinical examination of the neck showed an infected induration also in the parotid region of the same side. Chest X-ray was again normal. Laboratory tests revealed further increase of leucocytes (25.0 x 10^9 / L) and CRP (28.2 mg / dL). The HIV test was negative. On the same day re-incision was performed extensively exploring the submandibultar triangle, parotid region, retromolar, retromandibular and pharyngeal spaces, and the infection-causing root of the lower third molar was extracted. The culture of the pus content indicated the presence of *Streptococcus viridans* and based on the antibiogram cefepime 2g /12 h i.v. was given.

Two days after the second incision, temperature raised to 38.3^{0}C with severe pain below right rib arch, major dysphagia and cough. Neck ultrasound and CT were performed then which showed a large formation of thick fluid content and gas distal from the a. carotis bifurcation bilaterally. The thoracic CT scan revealed equal pathological formation in the mediastinum (Figures 1, 2).

Emergency posterolateral left thoracotomy through the fifth intercostal space was performed and about 550 cm^3 of purulent material from the mediastinum was evacuated. Drains were placed, one in each of the three compartments of the mediastinum. During the same procedure wide incisions of the neck bilaterally were carried out, including the carotid spaces, suprasternal, parotid and parapharyngeal regions. Wide drains were placed on the neck bilaterally. The patient was transferred to the intensive care unit and attached to mechanical ventilation. Thromboprophylactic therapy was introduced and based on the cultures, 1 g / 12 h + amicacin sulphate 500 mg/12 h were given. In a few postoperative days,

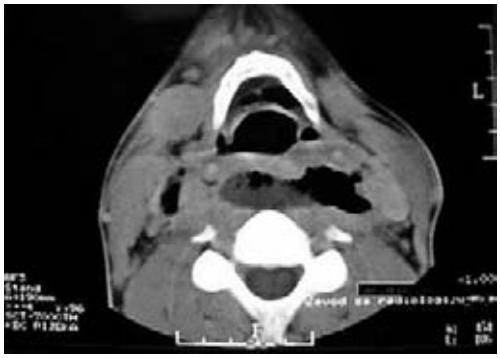

Figure 1. CT of the neck: fluid and gas collections in the retropharingeal compartments.

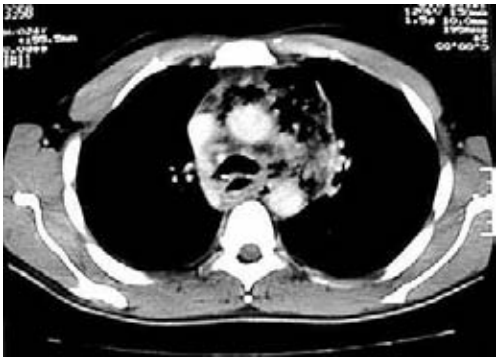

Figure 2. CT of the mediastinum: mediastianal purulence and clear lungs.

the patient was cardiocirculatory instable, with abnormal coagulogram, haematogram and hepatogram. Daily follow-up chest X-rays were performed, and on the 7th day after thoracotomy the follow-up chest X-ray showed lower transparency of lung lobes, indicating a follow-up thoracic CT was required. The CT scan demonstrated enormous bilateral pleural empyemas, with a marked reduction in respiratory space and a paracardial purulence (Figure 3).

Due to extremely worsened general condition of the patient, percutaneous bilateral thoracic CT-controlled drainage was performed, 1800 ml of pus was evacuated and a significant lung re-expansion was obtained. A suction drain was placed in each chest (Figure 4).

Antibiotic therapy was changed to vancomycin 1g /12 h + metronidazole 500 mg / 8 h (based on the cultures of purulent material obtained by drains). The patient's condition gradually improved. On the 22nd day after percutaneous drainage, chest drains were removed, and on the 25th day mechanical ventilation was removed. The patient was discharged from the intensive care unit after the total stay of 37 days, without any significant consequences except slightly muffled voice.

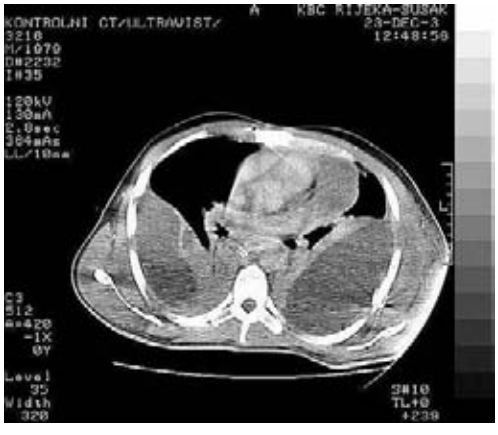

Figure 3. CT of the thorax: bilateral pleural empyema.

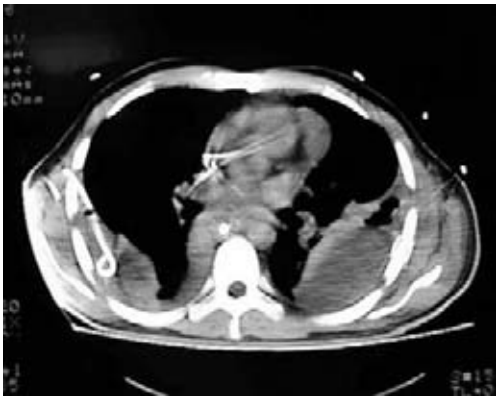

Figure 4. CT of the thorax after drainage: bilateral drains in the pleural space.

Discussion

This case demonstrates potentially disastrous effects of odontogenic infections. DNM is a rare result of a dental infection, and even more infrequently, bilateral pleural empyema develops as a complication of DNM.[1,3-7] In the period 1990-2004, there were no cases of mediastinitis after orodental or oropharyngeal infection in our epidemiologic centre which covers the population of about 400,000 people. Either due to a long period without serious complications of odontogenic infections (although an average of 50 patients with odontogenic abscess are admitted to hospital annually), or because the young man was previously completely healthy without a history of any disease or addiction, and palpation of the neck did not show a larger induration and relatively low fever considering the severity of the condition, this complication was diagnosed with a delay, which sometimes contributes to a high mortality rate of DNM. Estrere *et al.* report that one third of all cases of mediastinitis are diagnosed at post-mortem examination.[8] Symptoms of cough, dysphagia and dyspnoea, swelling of the neck and upper part of the chest with crepitance indicate clinical manifestations of mediastinitis, but these are late signs. Early diagnosis requires radiologic evaluation and CT is indispensable because clinical examination alone is reliable in only 55% of cases. Besides, CT is beneficial in postoperative follow-up of DNM.[1,6,9-12] The fact is that a delay in diagnosis of several days results in severe complications such as pyothorax, aortopulmonal fistula, sepsis, the erosion of the carotid artery or aorta, purulent pericarditis, DIC and multiple damages to the organs.[13] Our patient developed bilateral pleural empyema which is infrequently described as a complication of odontogenic DNM.[1,3-5,7] Inadequate surgical drainage can lead to deterioration of the patient's general condition and can cause new infectious foci in residual abscesses. Therefore, the meticulous drainage of the abscess, coupled with antibiotics and γ-globulin as supportive therapy.[13,14] is mandatory. For minor infections, most authors recommend penicillin and metronidazole *per os* for 7 days as the first- line therapy in out-patients. For major infections, authors suggest penicillin G 4 million units every 6 h i.v. together with metronidazole 500 mg every 8 h i.v., and against gram- negative species additional gentamicin 3 mg/kg i.v. every 24 h.[15,16,17] Maisel and Karlen recommend simultaneous administration of the third generation of cephalosporin and clindamycin or metronidazole as initial antimicrobial coverage until the results of the antibiogram are obtained.[18]

The approach to the drainage of mediastinum remains a moot point. Nevertheless, in case of a massive infection transthoracic approach is required.[1,6,8,10,12,13,19] Posterolateral thoracotomy provides adequate drainage of all portions of the mediastinum, pleural cavity and pericardium. One of the issues is also to perform tracheostomy immediately or to leave a tracheal tube. Our patient had a tube during the whole treatment with mechanical ventilation. Many authors prefer immediate tracheostomy in major cervical infections, to prevent the risk of additional intubations after accidental dislodgement of endotracheal tube in head movements. Other authors prefer intubation in all cases without respiratory impairment since opening of the airway by tracheostomy can result in the propagation of infection to the lungs. Opening cervical fascia in tracheostomy exposes the patient to the contamination of pretracheal space and to the risk of caudal spread of the infection to the mediastinum.[6,8,12,19-22]

According to the literature cervical infections are more common in immunosuppressive patients[8] but Mathieu *at al.*[23] re-

ported that 58% of cases necrotizing fascitis develop in previously healthy patients like in described case.

Although DNM as a complication of dental infection is thought to be an infrequent clinical entity, according to Sakamoto *et al.*, DNM strictly related to oral causes accounts for 60-70% of all reported cases.[22] Usually it originates in the second or third mandibular molar, which roots lie below the mylohyoid muscle providing the infection with a possibility of an immediate access to the submandibular space.[8, 24, 25] In our patient, the third molar was involved.

With a view to all this, in the case of the patient reported here, there were several pointers which indicated the possibility of this complication. Out- patient treatment in the dental office took some time with questionable need for trepanation of less valuable residual root of the third molar. Even on admission of the patient, the presenting clinical signs and laboratory findings should be followed by CT scan, which was delayed due to underestimation of the patient's condition, although he was eventually successfully managed.

Conclusions

Early diagnosis, aggressive drainage and antibiotic therapy with adequate postoperative care can save a patient with DNM, despite a high mortality rate of this disease.

Therefore, practitioners who face cases of odontogenic infection must be aware of this severe complication even in previously healthy patients, and together with adequate knowledge of this entity, must be able to recognize prodromal symptoms of the disease and if DNM is suspected to perform CT examination.

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images in clinical medicine

Basal cell carcinoma on the left cheek

Boris Jančar

Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia

A 91-year-old female patient was treated with irradiation for histologically confirmed basal cell carcinoma on the left cheek. The tumour, measuring 3 x 3 cm, with the depth of 2 cm, was extending up to the lower lid of the left eye (Figure1). Due to old age and poor physical condition, the patient was irradiated once a week in altogether three treatment sessions. She received a total equivalent dose of 70 Gy. On the follow-up control performed 9 months after the completed radiotherapy, it was noted that the tumour regressed completely. The photo was taken 21 months after irradiation (Figure 2).

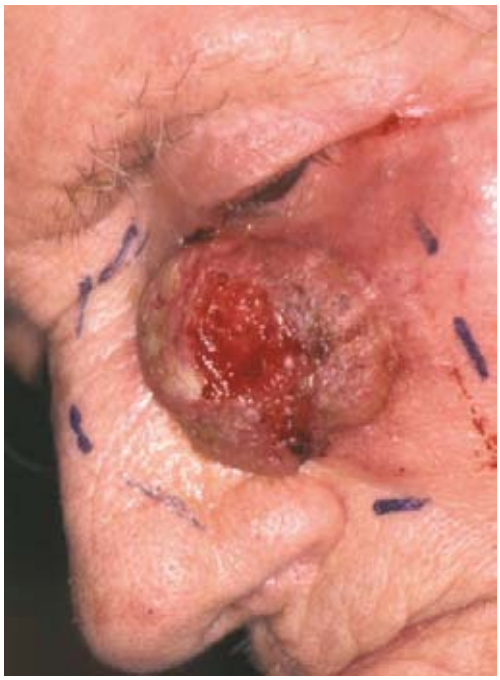

Figure 1. Basal cell carcinoma on the left cheek.

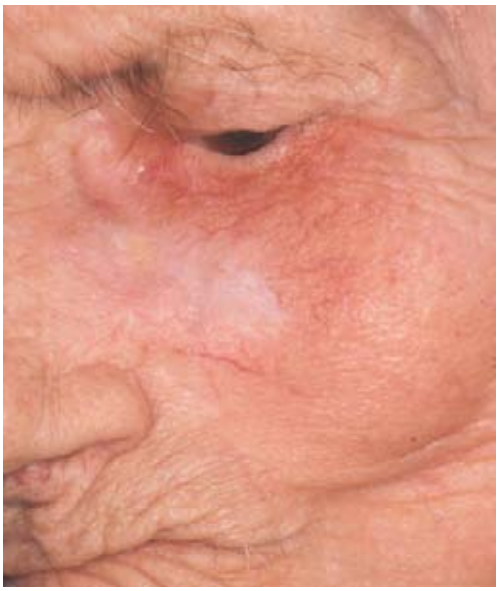

Figure 2. Left cheek 21 months after radiotherapy.

The patient died from heart failure at the age of 94 years, 29 months after the completed therapy. At the time of her death, no recurrence of basalioma was observed.

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Correspondence to: Prim. Boris Jančar, MD, MSc, Department of Radiation Oncology, Institute of Oncology Ljubljana, Zaloška 2, Ljubljana, Slovenia; Phone; + 386 1 5879 295; Fax: + 386 1 5879 295; E-mail: bojancar@onko-i.si

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Kidney cancer

Mirjana Rajer

Department of Radiotherapy, Institute of Oncology Ljubljana, Slovenia

Background. *The purpose of this paper is to present the epidemiology, diagnostic workup and treatment of renal cell carcinoma (RCC) with an emphasis on the Slovenian epidemiological data. RCC represents 2% of all cancers and is the third most common genitourinary tract tumour. It most frequently occurs among people of ages, between 50 and 60 years. Male patients are more prone to it than female. A number of environmental, occupational and genetic factors have been found to be associated with the development of RCC. Patients often have nonspecific symptoms and this is the reason why for half of them the disease is already metastatic when diagnosed. The most common sites of metastases are lungs (75%), followed by soft tissues (36%), bones (20%), liver (18%), skin (8%) and central nerve system (8%). In the evaluation of RCC multiple diagnostic procedures are needed with obligatory image diagnostics.*

Conclusions. *Radical nephrectomy is still the mainstream treatment of localized disease. Nephron sparing techniques have been used in cases, where radical operation would result in an anephric patient. Efficient adjuvant therapy has not been discovered yet. Until recently interpherone and interleukin were the only known effective treatments for metastatic disease, but now new and more efficient biologic agents are being discovered. The most important prognostic factor for survival is stage at the beginning of treatment. The 5-year survival rate is 95% for patients with stage I disease, 88% for stage II, 59% for stage III and 20% for stage IV.*

Key words: carcinoma, renal cell – epidemiology – diagnosis – therapy; nephrectomy; survival analysis

Epidemiology

General notes

Renal cell carcinoma RCC (e.g. hypernephroma, Grawitz's tumour) accounts for approximately 2% of all cancers. It is the third most common genitourinary cancer. The other two are prostatic and bladder cancer.[1] Over the past 65 years its incidence has been constantly growing with an annual rate of 2-4%.[2,3,4] The reason for this rise is unknown.[3] This type of cancer is more common among people of age between fifty and seventy years. Male patients are more prone to it than female patients.[2] The ratio male to female patients is 1.5 : 1.[3,4] People in urban environments a have higher incidence of RCC than those in rural.[4]

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Correspondence to: Mirjana Rajer, MD, Department of Radiotherapy, Institute of Oncology Ljubljana, Zaloška 2, 1000 Ljubljana, Slovenia; Phone: + 386 41 26 99 46; Fax.: + 386 1 587 9 400; E-mail: mrajer@onko-i.si

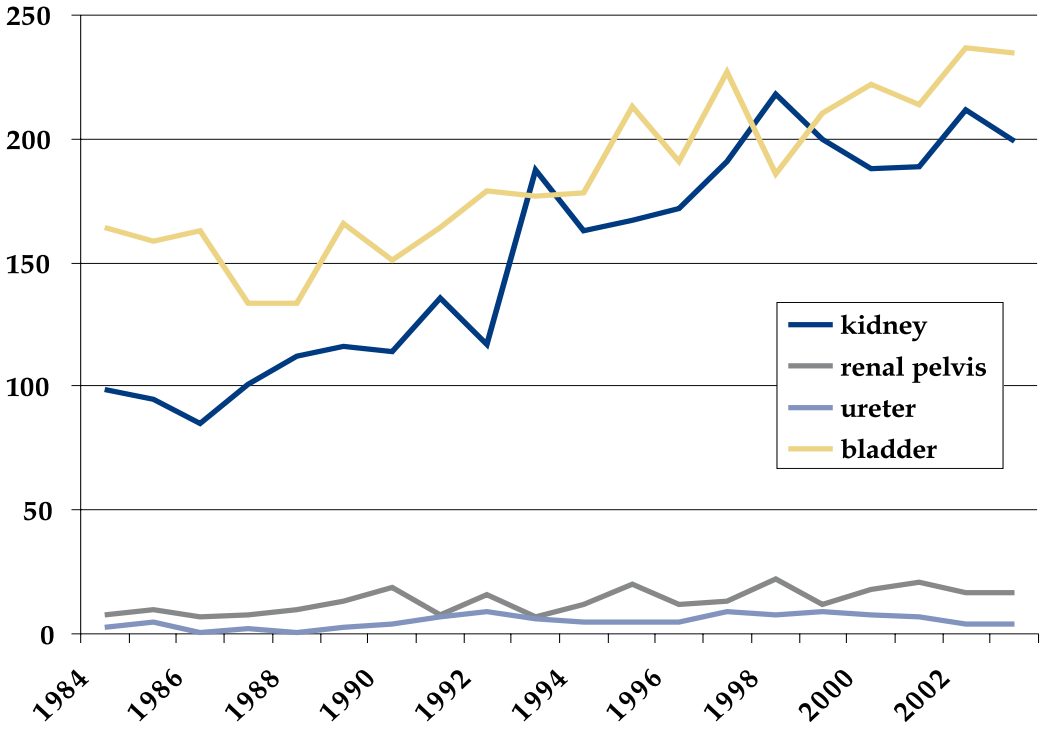

Figure 1. Newly diagnosed urinary tract tumors by site (1984-2003).

Slovenian epidemiological data

Data from the Cancer registry of Slovenia show that in the past twenty years the number of kidney cancers has been constantly rising as has the number of bladder cancers, while the number of newly diagnosed tumours of renal pelvis and urether remained approximately the same during this period (Figure 1).[5]

In the year 2003 there were 9997 newly diagnosed cancers in Slovenia (5026 of them among men and 4971 among women). In the same year the number of new cases of renal cancer was 193 (121 male patients and 72 female). Incidence for 2003 was 12,4 for males and 0,7 for females. Figure 2 shows the number of new renal cancers by gender.[5]

Renal cancer is the tenth most common cancer among Slovenian males and accounts for 2.4% of all male cancers. Others, in order by incidence, are: lung cancer, colorectal cancer, prostate cancer, head and neck cancer, melanoma, bladder and pancreatic cancer. Kidney cancer is not among the ten most frequent cancers in females, which are: breast cancer, cancer of the skin, colorectal cancer, cancer of the uterus, lung cancer, cervical cancer, stomach cancer, ovarian cancer, melanoma and non Hodgkin lymphoma.[5]

The average age at diagnosis is 55 to 60 years and the ratio of the male to female patients is 1 : 1.5,[5] which is the same as the general average reported in literature.[3,4]

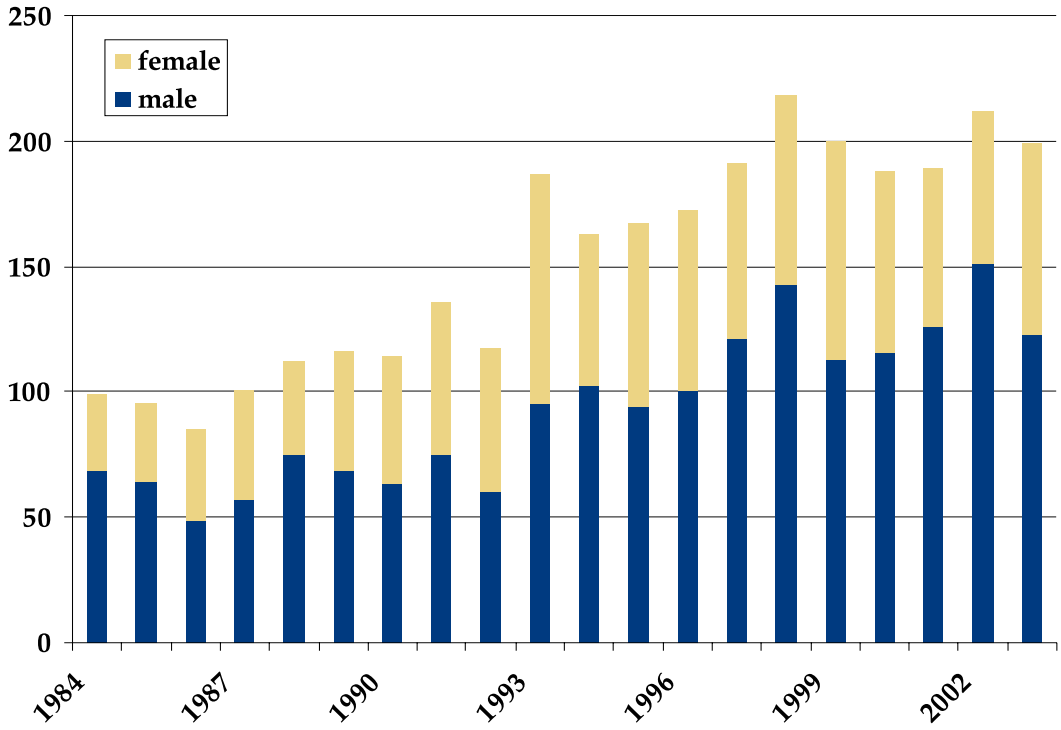

Figure 2. Number of newly diagnosed kidney cancers by gender (1984-2003).

Risk factors

A number of risk factors have been associated with RCC.[1] One of the most important is tobacco use. It is estimated that 30% of RCC in men and 24% in women are associated with smoking.[4] Exposure to some environmental factors can also lead to the development of RCC. These factors are exposure to cadmium, thorium dioxide, asbestos and petroleum products. People in certain professions are more at risk (e.g. leather tanners, shoe workers and asbestos workers). Other risk factors are hypertension, obesity, and long term use of analgesics, particularly those containing phenacetin.[1,2]

A special group of patients are those with end stage renal disease. These patients have a 100-fold greater incidence of RCC which is associated with development of acquired polycystic disease and the hyperplasia of the epithelium in these cysts.[4]

The relation between these factors and the development of RCC is weak, so that primary prevention seems to be quite ineffective. An effective screening system has not been developed yet, because of the relatively low incidence of RCC and the lack of simple diagnostic procedures.[2]

RCC occurs in sporadic and hereditary form. The most studied form of hereditary RCC occurs as a part of von Hippel-Lindau syndrome (VHL). VHL syndrome is a hereditary cancer syndrome caused by a mutation of the VHL gene. Affected individuals are at risk of developing tu-

mours in a number of organs including the kidney.[3,4] As many as 28-45% people with von Hippel-Lindau disease develop RCC.[1] In hereditary syndromes, people are affected at a younger age and tumours tend to be bilateral. More renal cancer occurs among people with autosomal dominant polycystic kidney disease and with tuberous sclerosis.[4]

Natural history

RCC may spread by local infiltration trough the renal capsule to involve the perinephric fat and Gerota's fascia or may grow directly into the renal vein (21% of cases) or vena cava (4% of cases). Lymph node metastases are most often found in the renal hilar, paraaortic and paracaval nodes.[1]

At the time of diagnosis, the disease is localized in 45% of patients, locally advanced in 25% of patients and metastatic in 30% of patients.[1,4] About half of patients with RCC develop metastases some time in the course of the disease. The most common site of metastases are the lungs (75%), followed by soft tissues (36%), bones (20%) liver (18%), skin (8%) and CNS (8%).[1]

Spontaneous regression of the tumour has been reported. The reason is probably immunogenic. The same phenomenon was observed with metastases after nephrectomy. The enthusiasm vanished when the review of literature showed that less than 1% of the patients experience it. This is the reason why nephrectomy is not recommended for this purpose any more.[1,4]

Pathologic classification

RCC is a tumour of the renal cells which develops from the proximal renal tubular epithelium.[4] The most common histological diagnosis is clear cell carcinoma which represents 85% of tumours.[3,4] Others are: papillary carcinoma (10%), chromofobic carcinoma (5%), carcinoma of Belliniy's duct (<1%) and the extremely rare carcinoma of medullary cells.[2,3]

Presentation

For almost half of patients the disease is advanced at the time of diagnosis. Most of them have some nonspecific symptoms like fatigue, weakness, nausea, night sweating and fever.[2,3] The classical triad which consists of flank mass, haematuria and pain in the lumbal area is rare, present only in the 1-5% of patients. It is a sign of advanced disease.[2,3] The most frequent symptom is either gross or microscopic haematuria.[1]

In some cases a large tumour growth has been reported. Such tumours can grow to the retroperitoneum without causing any symptoms.[4]

Lately more and more RCC are being discovered incidentally, while patients have some form of radiological diagnostic procedure. These tumours have a better prognosis because of the lower stage at detection.[1-4]

Less frequently patients present with signs or symptoms resulting from a metastatic disease, like bone pain and pulmonary symptoms.[3]

One of the most common signs is anemia due to haematuria or haemolysis. It has been observed in 30-88% of patients with RCC. Other signs are polycitemia, nonmetastatic hepatic dysfunction and acquired dysfibrinogenemia.[4]

RCC can also cause paraneoplastic symptoms. A lot of substances have been detected at an elevated concentration in patients with RCC: parathyroide like hormones, erythropoietin, rennin, gonadotropins, placental lactogen, prolactin, enteroglucagon, insulinlike hormones, adrenocorticotropic hormone and prostaglandins.[1]

Diagnostic workup

Image diagnostics is a part of the initial workup. Beside ultrasound examination, the mostly recommended are CT (with and without the contrast) or MRI of the abdomen and pelvis. CT is a very good method for the assessment of the lymph node status. The use of CT contrast has improved its sensitivity in detecting very small tumours. MRI is preferred to CT in cases where involvement of the inferior vena cava is suspected or instead of the CT when there are contraindications to the administration of the contrast material. When there is suspicion of the involvement of the inferior vena cava, an US with colour flow Doppler should be performed to determine the position of the tumour thrombus and to help the surgeon with the surgery planning.[3,4] US has replaced the previously used venacavography. Sometimes other studies are needed to asses the tumour, like intravenous pyelogram, renal arteriogram and cyst puncture with fluid cytology.[1]

For the optimal staging and planning of the surgery multiple diagnostic procedures are recommended.[4]

Imaging of the chest, either CT or radiography should be performed for assessment of the stage of disease.[3] When a patient complains of bone pain or has an elevated serum alkaline phosphatase, the suggested test is a bone scan which is not performed routinely otherwise. The same holds for the CT or MRI of the brain, which is to be performed if brain metastases are suspected. PET is not considered as a routine diagnostic procedure.[3]

Treatment

Treatment of localized disease

Surgical treatment is considered the only effective treatment for the localized disease. The preferred operation is a radical nephrectomy which consists of removal of the kidney, perirenal fat, regional lymph nodes and ipsilateral adrenal gland. The removal of the regional lymph nodes is not a therapeutic procedure, but is being performed for staging purposes. Patients, who have metastases at their lymph nodes, tend to sub sequentially relapse with a distant metastases despite lymphadenectomy.[3,6]

Nephron sparing surgery (NSS) was originally considered only when radical operation would result in a patient requiring dialysis, such situations are:[3]

– RCC in a solitary kidney,
– Bilateral synchronous RCC,
– RCC in one kidney and inadequate functioning of the other.

Recently NSS gained a role in the treatment of small tumours (less than 7 cm in diameter) with equivalent results to the radical nephrectomy. Not all tumours are appropriate for NSS, but only those in the upper or lower pole and in the peripheral location.[3]

After surgical treatment 20-30% of patients experience a relapse, most commonly in the lungs. The median time to relapse is 1-2 years after surgery. Time to relapse is associated with the length of survival after the relapse.[3]

Adjuvant systemic treatment proved not to be effective and the same holds for adjuvant radiation therapy. Patients, to whom adjuvant radiation therapy has been administered, did not have a better survival or locoregional disease control compared to the non-irradiated patients despite characteristics which in other cancers require adjuvant radiotherapy. These are: incomplete tumour resection or metastatic lymph nodes found at the operation. This leads to the conclusion that after the nephrectomy observation of the patients is the only reasonable option.[3]

Treatment of advanced disease

Advanced disease (stage IV) is incurable and the intent of therapeutic proceedings is to prolong life, to reduce patient's symptoms and to improve the quality of life.[3]

Patients with resectable RCC and a solitary resectable metastasis are candidates for nephrectomy and metastasectomy. This holds for patients with synchronous discovery of NCC and metastatic site and also for the patients who develop metastases after neprhrectomy. Sites of metastases which are amenable for such management are bone, brain and lung. Most patients treated with metastasectomy experience a relapse at some time. However, some long disease free intervals have been detected.[3]

Some patients with metastatic disease benefit from cytoreductive surgery before the start of chemotherapy. These are patients with lung metastasis only, patients with a good performance status and those with good prognostic features.[3]

Kidney cancer is one of the few cancers in which systemic chemotherapy and hormonal therapy do not have a substantial benefit. The reason for this seems to be a big expression of the p glycoprotein. This is a protein in the membrane of the renal tubules and renal cancer. The function of this protein is to expel toxic lypofilic substances from the cell, and only those chemotherapeutics that are not the substrate for this glycoprotein, have some effect.[2]

Until recently the only effective systemic treatment was with interferone-α or IL-2. In both of these drugs the response rate is 30%, the median survival is 13 and 12 months respectively. These drugs have substantial undesirably side effects, which can be acute or chronic.[2]

Recently the FDA (Food and drug administration) approved 2 kinase inhibitors sunitinib and sorafenib for the treatment of metastatic RCC. Escudier *et al*. presented the results of a phase III study with sorafenib. Patients who progressed on the immunotherapy were randomized into two groups, those who received sorafenib and placebo. Progression free survival was 24 versus 12 weeks. Some degree of response was observed in 78% of the patients. Good response rates were also observed with the administration of sunitinib. Motzer *et al*. reported a 40% partial response rate, when sunitinib was administered as a second line treatment after patients progressed on the cytokine therapy. In another study patient were randomized to receive either a sunitinib or IFN-α as a first line therapy for methastatic disease. The median progression free survival was 47.3 in the sunitinib group and 24,9 weeks in the IFN group and the objective response rates were 35,7% and 8,8%.[3]

Other patients not suitable for the systemic therapy require a good palliative care which should include good pain management, and some of the procedures like radiation of painful methastatic sites or palliative nephrectomy in the cases of severe haematuria.[3]

Survival and prognostic factors

Survival of patients differs according to the initial stage of the disease which is the most important prognostic factor.[2] Patients who have tumours confined to the kidney, have much better prognosis than those with locally advanced or methastatic disease at the time of diagnosis. Table 1 presents 5-years survival rates in different stages of the disease.[1,4]

Metastatic disease is incurable and the duration of survival depends on the number and site of metastases.[2] Patients who have bone and CNS metastases, have a shorter survival time than patients with other metastatic sites. Other factors that influence (shorten) the survival are:

Table 1. 5-year survival of patients with RCC according to stage of the disease

Trial	Total No. of patients	Stage I	Stage II	Stage III	Stage IV
		5-years survival rate			
Robson	88	66	64	42	11
Skinner	309	65	47	51	8
Waters	130	51	59	12	0
Boxer	not known	56	100	50	8
McNichols	506	67	51	34	13
Cherrie	not known	not known	not known	50	0
Selli	115	93	63	80	13
Bassil	not known	91-100	not known	not known	18
Golimbu	326	88	67	40	2
Javidan	381	95	80	59	20
Dinney	314	73	68	51	20
Guinan	337	100	96	59	13
Kinouchi	350	96	95	70	24
Tsui	643	91	74	67	32

– bad patient performance status
– high degree of weight loss
– short disease free interval from the beginning of the treatment to the manifestation of metastases and
– some laboratory findings like high LDH values or low haemoglobin level.[2,4]

Another prognostic factor is the grade of the tumour. As expected tumours of the lower grade have a better prognosis.[2,3]

Incidentally found tumours have a generally better prognosis as they are being discovered at a lower stage. Five year survival rate of these patients is close to 100%.[1]

Conclusions

Survival statistics for RCC have not changed for the last 25 years. This is due to the fact that an effective adjuvant therapy for the locoregional disease has not been discovered yet, and that until recently there were only few possibilities of an effective systemic treatment for metastatic disease.[1] With the progression in diagnostics, surgery, new radiotherapy techniques and the discovery of the new biological therapies which are more effective and less toxic, major changes of the therapeutic results are expected. In spite of this, RCC still remains a big challenge for future research.

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case report

Case report from Mayo Clinic: Locally advanced Bartholin gland carcinoma

Melva E. Pinn*, Laura M. Austin*, David A. Schomas, Robert C. Miller

Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota, USA

Tumors of the Bartholin gland are rare, comprising less than 5% of all vulvar malignancies. Treatment is largely based on that of vulvar and anal squamous cell carcinomas. A case of invasive, grade 4, poorly differentiated squamous cell carcinoma of the Bartholin gland is presented. Our patient, a 47-year-old woman, had a history significant for cervical intraepithelial neoplasia treated with conization, type 2 diabetes mellitus, and tobacco use. The course of treatment included preoperative radiotherapy plus 5-fluorouracil and cisplatin chemotherapy, followed by restaging and posterior exenteration in combination with vaginal reconstruction.

Key words: vulvar neoplasms – radiotherapy – drug therapy – surgery – Bartholin gland

Introduction

Accounting for less than 5% of all vulvar malignancies, primary carcinoma of the Bartholin gland is rare. Cancers arising in the Bartholin duct are most commonly adenocarcinomas or squamous cell carcinomas; occasionally transitional cell, adenosquamous, and adenoid cystic carcinomas may develop. A case of locally advanced Bartholin gland carcinoma was seen recently at Mayo Clinic.

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*Visiting medical students at the Department of Radiation Oncology.

Correspondence to: Robert C. Miller, MD, MS, Division of Radiation Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: miller.robert@mayo.edu.

Case Report

A 47-year-old woman first noted a lump in the region of the introitus and labia majora in February 2006 and was evaluated by her local gynecologist. Her only symptom, other than mass effect, was minor constipation.

On examination under anesthesia, the patient was found to have a 5- to 7-cm by 7-cm mass that was believed clinically to arise from the region of the left-sided Bartholin duct. It was located anterior to the rectum and posterior and lateral to the vagina and extended to the region of the rectal sphincter. There was no involvement of the vulva, vaginal mucosa, or cervix on physical examination. A 2-cm mass was palpable in the left groin.

The patient underwent an extensive multimodality and multispecialty evaluation. Magnetic resonance imaging showed

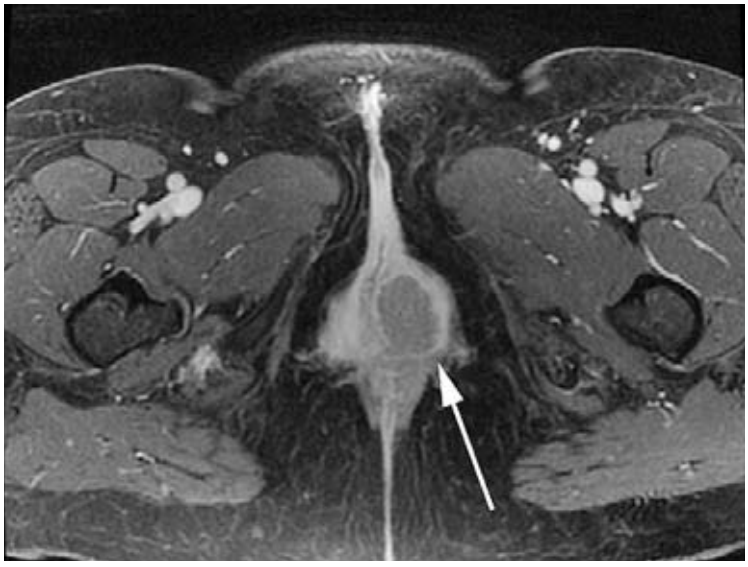

Figure 1. Axial T1-weighted magnetic resonance imaging before radiotherapy shows the primary Bartholin tumor (arrow).

a 5.1×3.8×4.5-cm lobulated enhancing mass arising between the vagina and rectum which appeared to encase the anterior and left lateral walls of the rectum (Figure 1). Perirectal lymph nodes of up to 1.6 cm were noted, as was a 2.0×1.5-cm enhancing lymph node in the left inguinal region, consistent with metastatic disease. Computed tomography (CT), chest radiography, and positron emission tomography (PET)/CT indi-

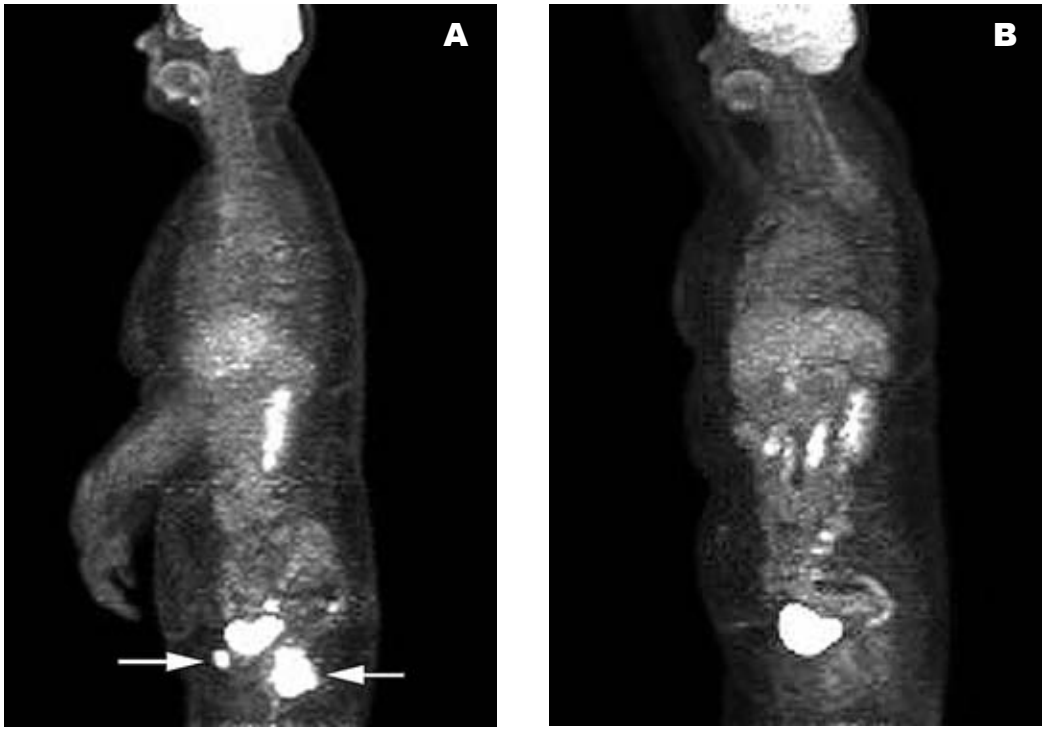

Figure 2. Lateral ^{18}fluorodeoxyglucose (FDG)–positron emission tomography. A, Image before treatment. Arrows show location of the left inguinal nodal metastases superiorly and primary tumor inferiorly. B, Image 1 month after radiotherapy and chemotherapy showing a complete response by FDG signal.

Table 1. Intensity-Modulated Radiotherapy Prescription

Tumor dose	Description	Normal tissue constraints
PTV 51.25 Gy in 2.05-Gy fractions	Gross tumor volume (including primary tumor, gross perirectal adenopathy, and gross inguinal adenopathy) + 13- to 15-mm margin	Bladder $V_{51.25Gy}$ <2% V_{40Gy} <30%
PTV 45.00 Gy in 1.80-Gy fractions	Radiographically uninvolved pelvis (excluding bladder and small bowel) and presacrum below the level of the bifurcation of the iliac vessels, and bilateral inguinal and external iliac lymph nodes	Small bowel $V_{51.25Gy}$ <2% V_{45Gy} <15% V_{30Gy} <20%
PTV 42.50 Gy in 1.70-Gy fractions	Common iliacs and presacrum to the mid L5 level	Perineum V_{52Gy} <2% V_{20Gy} <20% Femoral heads V_{45Gy} <2% V_{35Gy} <20% Uterus (used as an avoidance structure to conform dose to pelvis and nodal structures) $V_{51.25Gy}$ <2% V_{40Gy} <30%

PTV, planning target volume; V, volume.

cated no evidence of distant metastases (Figure 2 *A*). Endoscopic ultrasonography showed numerous abnormal perirectal nodes that were round and echopoor and measured from a few millimeters to 1.2 cm in diameter. The tumor involved the anterior portion of the anal sphincter mechanism.

Transrectal biopsy of the primary tumor in February 2006 indicated invasive, grade 4 (of 4), poorly differentiated squamous cell carcinoma. The neoplastic cells were strongly reactive for CK7 and showed normal staining for MLH1, MSH2, MSH6, and PMS2. The tumor lacked staining for CK20, CDX2, and estrogen receptor.

The patient's medical history was significant for cervical intraepithelial neoplasia treated with cervical conization in 1981. Additionally, the patient had a history of tobacco use and type 2 diabetes mellitus controlled with oral medications. She had never received radiotherapy or chemotherapy.

The departments of radiation oncology, medical oncology, gynecologic surgery, and gastroenterology were consulted regarding treatment; it was believed that the optimal course of treatment would involve preoperative radiotherapy and 5-fluorouracil (5-FU) and cisplatin chemotherapy, followed by restaging and posterior exenteration in combination with vaginal reconstruction.

In March 2006, the patient began concurrent chemotherapy and intensity-modulated radiotherapy (IMRT) to a total dose of 51.25 Gy in 25 fractions to regions of gross

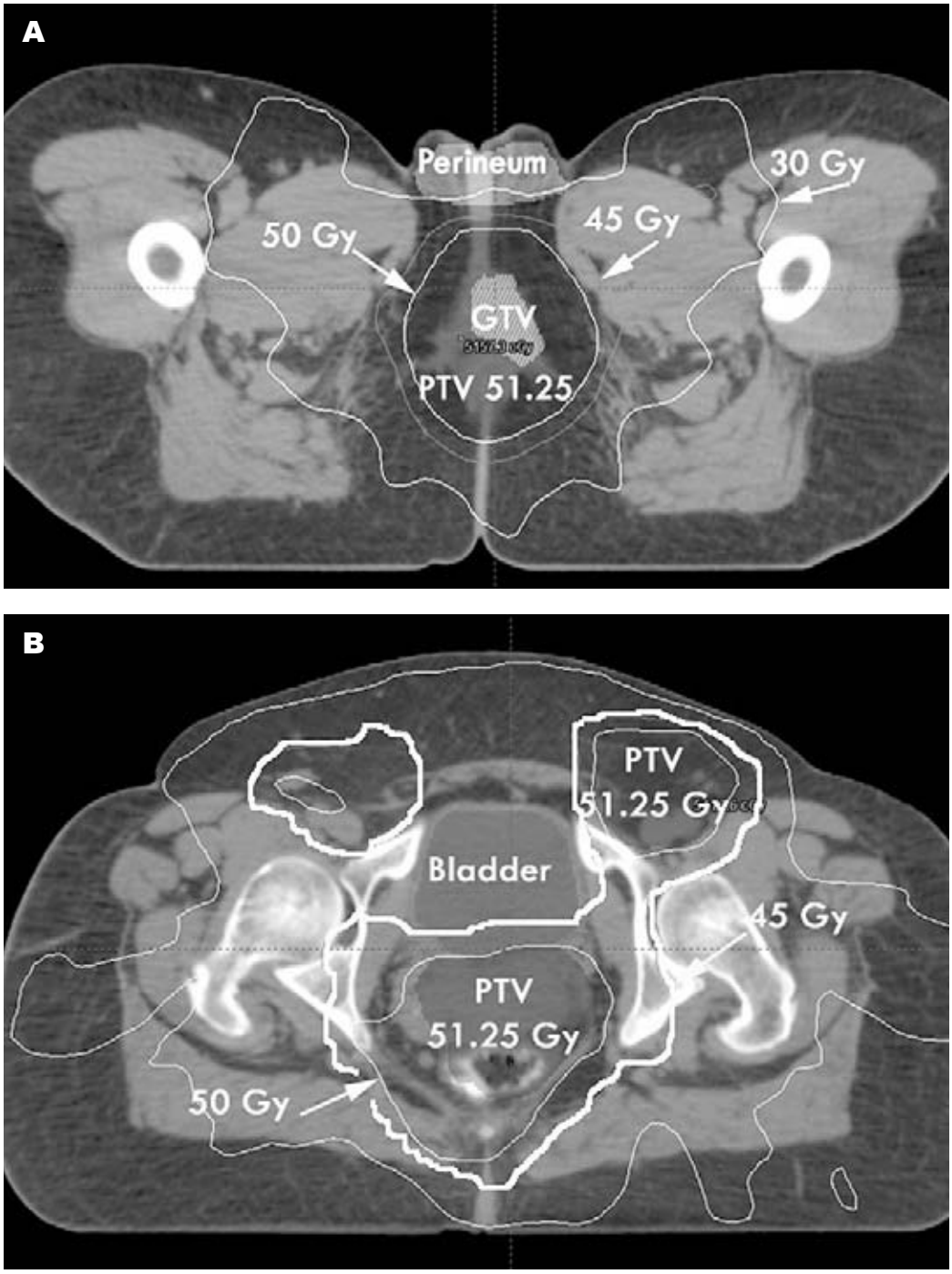

Figure 3. Intensity-modulated radiotherapy isodose curves showing relative sparing of the perineum (*A*) and sparing of the bladder and central pelvis (*B*). (Planning target volume [PTV] 45.00 Gy and femur volumes deleted for clarity of illustration.) GTV, gross tumor volume.

tumor, with margins involving the Bartholin gland region and the perirectal and left inguinal adenopathy. IMRT was delivered with 6-MV photons after a CT simulation of the patient in a supine, frog-legged position with a full bladder. Full technical details of the IMRT prescription are shown in Table 1. All 3 planning target volume (PTV) dose levels were treated simultaneously (Figure 3). The patient received 2 cycles of cisplatin and 5-FU chemotherapy intravenously over 4 days in weeks 1 and 4 of radiotherapy. Cisplatin was given at 75 mg/m^2 on day 1 of each chemotherapy cycle, and 5-FU, by ambulatory continuous venous infusion over days 1 through 4 at 225 mg/m^2 per day. The patient had radiation toxicity (by the Common Terminology Criteria for Adverse Events v3.0) consisting of grade 3 dermatitis, grade 2 leukopenia, grade 2 dysuria and frequency, and grade 3 enteritis and proctitis.

She was able to complete the prescribed course of radiotherapy and chemotherapy within 32 days total time, despite the acute toxicity. The patient returned for re-evaluation approximately 4 weeks after completion of radiotherapy and chemotherapy, at which time the acute toxicity had resolved. Physical examination showed complete resolution of the primary tumor, and pelvic examination showed no evidence of abnormalities. A PET/CT study indicated no ^{18}fluorodeoxyglucose uptake at the site of the primary tumor and lymph nodes, no evidence of the left inguinal adenopathy, and near resolution of the primary tumor and perirectal lymphadenopathy by PET tracer uptake (Figure 2 B).

The patient then underwent posterior exenteration and vaginal reconstruction with a vertical rectus abdominis muscle flap. Pathologic review of the resected specimen showed no residual tumor. An ill-defined submucosal mass was seen in the region of the anterior rectal wall showing fibrosis and histiocytic inflammation but no evidence of tumor. Nine lymph nodes were negative for tumor. The groin was not dissected at the time of surgery.

The patient returned for re-evaluation 5 months after surgery. Her postoperative course had been unremarkable. She reported no pain or gastrointestinal tract, skin, or genitourinary symptoms. Physical examination showed no evidence of recurrent tumor, in either the groin or the pelvis. No lower extremity edema was present. CT performed 1 month after surgery showed no evidence of pathologic processes other than postoperative changes associated with the resection and muscle flap. She will undergo re-examination in our clinic approximately every 12 weeks for 2 years, then every 6 months for 3 years, and yearly thereafter.

Discussion

The incidence of Bartholin gland tumors is highest among women in their 60s, with the median age of diagnosis being 57 years. Most patients with a Bartholin gland malignancy do not have a history of other Bartholin gland disorders. Bartholin gland enlargement in a postmenopausal woman should raise suspicions of malignancy because benign inflammatory disease typically does not occur in this age group. A biopsy should be performed for any abnormal growth of the Bartholin gland if the patient is older than 40 years.

The differential diagnosis for a Bartholin gland tumor most commonly includes cysts and abscesses, which occur in 2% of women, and other vulvovaginal disorders, such as vulvar carcinoma, acrochordons, hidradenomas, other dermatoses, and condyloma acuminata. The Bartholin gland is composed of columnar epithelium, and the ducts are lined by stratified squamous epithelium, which changes to transitional

cell epithelium toward the terminal ducts. Squamous cell carcinoma is the only lesion of the Bartholin gland linked to human papillomavirus. Metastases are common as a result of the copious supply of vascular and lymphatic networks in the area. The most common presentation of a Bartholin gland carcinoma is a painless vulvar mass.[1,2]

Few data are available on the associated treatment of Bartholin gland carcinoma; such treatment is largely based on that of vulvar and anal squamous cell carcinomas. No large randomized controlled trials have been published on the treatment of advanced vulvar cancer. Moore *et al.* [3] reported a phase II study by the Gynecologic Oncology Group examining the use of preoperative chemoradiotherapy to avert the need for more radical surgery. In this study, 73 evaluable patients with clinical stage III-IV squamous cell vulvar carcinoma were treated with a planned split course: twice-daily concurrent cisplatin (50 mg/m^2) and 5-FU (1,000 mg/m^2) on days 1 through 4 and radiotherapy (to 47.6 Gy), followed by surgical excision of the residual primary tumor plus bilateral inguinofemoral lymph node dissection. A total of 33 patients had no visible vulvar cancer after combined chemoradiotherapy.[3] The authors concluded that preoperative chemoradiotherapy in advanced squamous cell carcinoma of the vulva is feasible and may decrease the need for more radical surgery.[3] In another study, Han *et al.* [4] concluded that concurrent chemoradiotherapy as primary treatment for locally advanced vulvar cancer decreases local relapse rate and improves disease-specific and overall survival versus radiotherapy alone.

Unlike vulvar cancers, treatment of anal cancer has been evaluated in several randomized controlled trials. At one time, abdominoperineal resection was considered the treatment of choice for anal cancer.[5] However, the standard of care has since become infusion chemotherapy with 5-FU and mitomycin C (MMC) along with radiotherapy (45-50 Gy). Surgery is now reserved as a last resort.[5] A phase III randomized controlled trial assigned 110 patients to either definitive radiotherapy alone or radiotherapy combined with 5-FU/MMC.[6] The patients received 45 Gy given in 5 weeks, followed by a 6-week rest period and then a 15- to 20-Gy boost to a total dose of 60 to 65 Gy. The chemotherapy regimen consisted of 750 mg/m^2 of 5-FU on days 1 through 5 and 29 through 33 and a single dose of MMC (15 mg/m^2) on day 1. Concurrent 5-FU/MMC with radiotherapy significantly improved the locoregional control rate and significantly decreased the need for colostomy.[6]

A study by the UK Co-ordinating Committee on Cancer Research had a similar design; 585 patients were randomly assigned to 45 Gy over 4 to 5 weeks alone or combined with chemotherapy (5-FU [1,000 mg/m^2 for 4 days or 750 mg/m^2 for 5 days by continuous infusion] during the first and final weeks of therapy and MMC [12 mg/m^2] on day 1).[7] The combined chemotherapy and radiotherapy arm had a significant increase in local control rate. The authors concluded that standard treatment for anal cancer should be a combination of radiotherapy and infusion of 5-FU and MMC.[7] A phase III randomized trial reported by Flam *et al.* [8] aimed to determine the importance of MMC in the combined treatment of anal cancer. The study showed significantly increased colostomy-free survival, disease-free survival, and local control rates. The authors concluded that despite greater toxicity, the use of MMC is justified.[8]

Our patient was treated with combined-modality therapy similiar to that used for patients in the study of squamous cell vulvar carcinoma by Moore *et al.* [3] One notable difference, however, was our use of IMRT. IMRT of the pelvis has been shown by numerous investigators to be safe, feasible,

and effective in terms of acute and chronic toxicities, as well as clinical outcomes.[8-12] Specifically, Garofalo *et al.* [13] evaluated IMRT planning in patients with vulvar cancer undergoing treatment to both the pelvic and inguinal fields. As compared with conventional techniques, IMRT was associated with a decreased volume of small bowel, bladder, rectum, and femoral heads receiving the prescription dose. Recently, investigators from the University of Chicago and Mayo Clinic Rochester have published their experience with IMRT and anal cancer, which showed favorable toxicity and clinical outcomes.[14-15]

With successful completion of aggressive combined-modality therapy using concurrent chemotherapy and radiotherapy, a surgically verified complete pathologic response was obtained in the patient presented here. However, metastases of the abdomen and liver eventually developed. At this time, decisions regarding salvage chemotherapy and other potential palliative measures are being considered for this patient.

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case report

Triple synchronous cancers: a medical and ethical problem

Lučka Debevec, Rok Cesar, Izidor Kern

University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia

Background. *In a patient with suspicious synchronous multiple tumours, there are limited possibilities for effective therapy. Therefore, the decision for invasive diagnostics and precise staging of tumours is questionable, especially in elderly patients suitable only for symptomatic therapy.*

Case report. *A 78-year-old man with hypertension and angina pectoris was admitted to the hospital due to syncope. Two primary lung tumours and a kidney tumour were detected by imaging investigation. The patient refused invasive diagnostics and left the hospital. After 19 months he was readmitted in an impaired clinical condition and subsequently died of bronchopneumonia. The autopsy revealed squamous cell carcinoma of the right upper lobe with metastases to regional lymph nodes and to the brain, small-cell carcinoma of the left upper lobe with metastases to regional lymph nodes and to the spleen, and clear-cell kidney carcinoma with multiple metastases to the lungs. All tumours were necrotizing, and therefore we assumed that any attempt at specific therapy would have been ineffective.*

Conclusions. *In an elderly patient with advanced lung tumors and suspicious synchronous triple cancers, the "wait and see" option can be suitable.*

Key words: neoplasms, multiple primary; prognosis; ethics, medical

Introduction

Multiple synchronous cancers in the same organ or in various organs are rather unusual. Sometimes this condition is diagnosed during the staging process of the tumour, by postoperative histology of a resected organ, but it is mostly identified by autopsy. During the diagnostic procedure involving the patient with suspicious multiple tumours, a dilemma appears relative to the precise staging of each of all probable tumours in a patient suitable only for symptomatic therapy.

A case of synchronous triple tumours is presented in which noninvasive diagnostic procedures were performed and suspicion of triple primary cancer was established. The patient refused invasive diagnostics and left the hospital. Fortunately, the course of the disease was rather favorable, and none of the three tumours caused symptoms requiring urgent invasive diagnostics or attempts at any specific therapies. Despite three disseminated carcinomas, the patient survived

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Correspondence to: Assist. Lučka Debevec, MD, PhD, University Clinic of Respiratory and Allergic Diseases Golnik, SI-4204 Golnik, Slovenia; Phone: +386 4 2569 100; Fax: +386 4 2569 117; E-mail: lucka.debevec@klinika-golnik.si

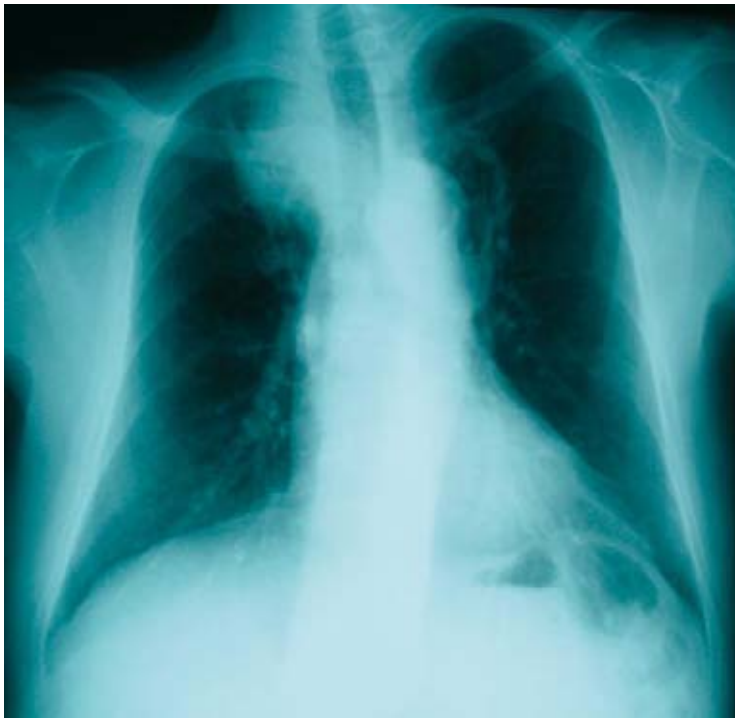

Figure 1. X-ray of the chest on the first admission (6 June 2005).

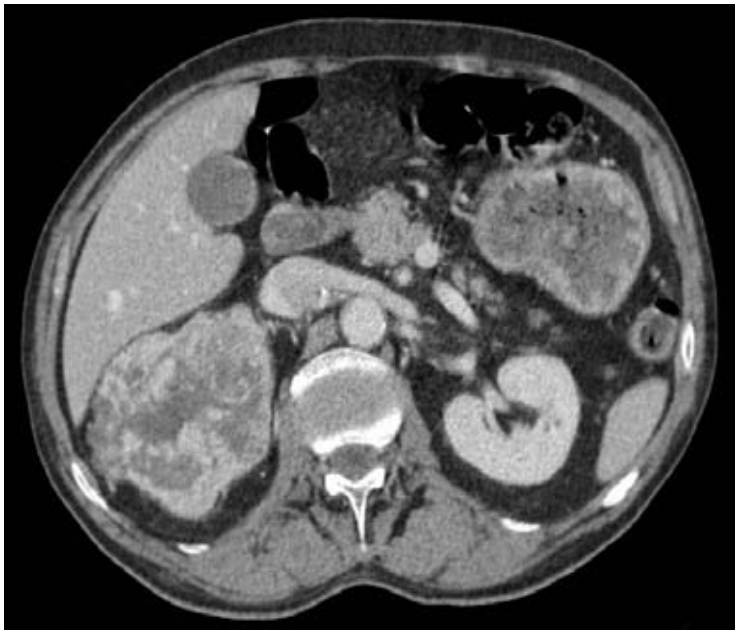

Figure 2. CT scan of the abdomen (9 June 2005).

at home, *i.e.* without specific or symptomatic therapy needing hospitalization, for 19 months after the diagnosis of two lung tumours and a kidney tumour.

Case report

A 78-year-old man with hypertension and angina pectoris was brought to the hospital due to syncope without convulsions in June 2005. At the time of admittance he had no fever but a dry cough. Laboratory tests indicated anemia (Hb 9.2 g/dL), leucocytosis (WBC 16.5 x $10^3/\mu L$), hypokalemia (potassium 3.4 mmol/L), slightly elevated BUN and creatinine, and low serum iron (2.7 μmol/L).

A CT scan of the brain showed diffuse atrophy without signs of metastasis. On the chest X-ray, tumours infiltrating in both upper lobes were visible. The lesion on the left side was excavated (Figure 1). A CT scan of the thorax and upper abdomen showed – in addition to tumour lesions in the left and right lung – also a tumour-enlarged right kidney (Figure 2). The conclusion after the im-

aging procedures was the probability of three synchronous primary tumours: a tumour in the right upper lobe infiltrating the mediastinum, a tumour in the left upper lobe with metastases to hilar and mediastinal lymph nodes, and a tumour in the right kidney.

The patient did not agree to further invasive diagnostics for verification of the tumours, and despite some persuasion he left the hospital with advice for a urological examination.

By the end of December 2006, the patient was admitted bedridden, dehydrated, somnolent, with respiratory insufficiency, anisocoria and anamnesis of frequent vomiting during the previous few days. Laboratory tests showed high inflammatory parameters (CRP 97.2 mg/dL, WBC 16.6 x $10^3/\mu L$), and elevated BUN (50.8 mmol urea /L) and creatinine (149 μmol/L), but there was no anemia (hemoglobin was currently 15.9 g/dL).

A brain CT showed cerebral atrophy and a coliquated round lesion in the right occipital region without surrounding oedema (Figure 3). On the chest X-ray, the

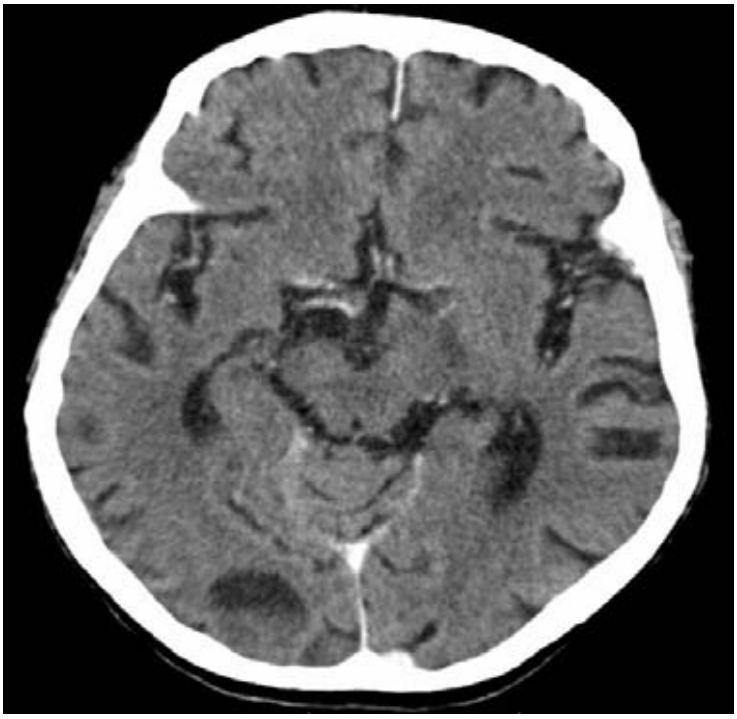

Figure 3. CT scan of the brain (28 December 2006).

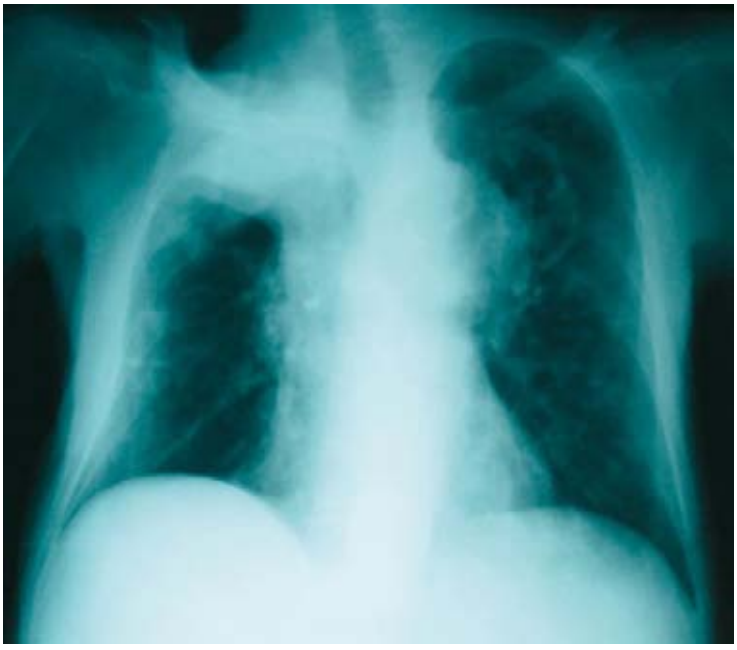

Figure 4. X-ray of the chest on the second admission (26 December 2006).

known tumours of the upper lobes and diffuse infiltrates in both lungs appeared (Figure 4).

The patient received antibiotics and parenteral hydration, and died four days after admittance.

The autopsy revealed the excavated tumour of the left upper lobe, 7 cm in diameter, infiltrating the left main bronchus, to be a necrotizing small-cell carcinoma with metastases to ipsilateral hilar and ipsilateral mediastinal lymph nodes, and with necrotizing spleen metastasis of 3 cm.

The tumour of the right upper lobe, 10 cm in diameter, was also necrotizing. Due to enlarged and coliquated hilar and mediastinal lymph nodes, there was an impression of tuberculosis. But histology showed a necrotizing squamous cell carcinoma of the right lung and lymph nodes, and a necrotizing metastasis of the same histology was revealed in the right occipital region of the brain.

The right kidney was entirely transformed by a 13 cm tumour infiltrating the renal capsule and perirenal fat tissue. Histology revealed a necrotizing well differentiated clear-cell carcinoma with multiple metastases to both lungs.

All three primary tumours as well the metastases of the brain, spleen, right hilar and mediastinal lymph nodes, were necrotizing. The cause of death was bronchopneumonia.

Discussion

In patients with two or more tumour lesions detected in various organs, one reasons that it is a primary tumour with metastases, which is statistically most probable. Synchronous triple tumours are uncommon. In the annual reports of the Cancer Registry of Slovenia it is not possible to determine the number of patients with multiple cancers, since these are registered as different single tumours, *i.e.* cancer cases, irrespective of the number of patients.[1] So, a triple cancer would be registered three times, despite involving the same patient. In the literature it is difficult to obtain data on synchronous cancers. Hamada *et al.*[2] reported a gradual increase of triple primary cancers in Japan in the period 1994-1996. The incidence of triple cancers represented 0.81% of all autopsy cases reported.

There are interesting site combinations of triple cancers. The most frequently reported were all tumours in the same organ or organ system: lung,[3-9] digestive organs,[10-13] and urogenital organs.[14-19] Lung cancer appeared in combination with tumours of two various organs: urinary bladder and esophagus,[20] breast and stomach,[21] pancreas and duodenum,[22] and stomach and thyroid.[2] Kidney cancer was seen in combination with tumours of the liver and oral floor,[23] sigmoid colon and thyroid.[24] On *PubMed* one can find articles on synchronous triple tumours, for all successfully resected ones, but mostly published in Japanese without an English abstract. Therefore, the many cases of synchronous triple cancers established in Japan raise the possibility of the influence of atomic bomb radiation on cancer incidence. Hakada *et al.*[17] mentioned that there had been a patient with synchronous cancers of the kidney, urinary bladder and prostate exposed to the atomic bomb explosion in Hiroshima in 1945.

In our patient presented above, it is questionable whether the disease could have progressed otherwise, even with the patient's agreement to invasive diagnostics at the time of first admittance to the hospital. Probably one or both lung tumours could have been established by bronchoscopy. A needle aspiration biopsy under ultrasound guidance would have been necessary for verification of the kidney tumour. Had there been successful definition of all primary tu-

mours, carefully dosed chemotherapy for lung cancer would parhaps have been applied. The kidney tumour would certainly not have responded to chemotherapy, and embolization of the renal artery would have been indicated, especially in the case of haematuria. Concerning the necrosis of all primary tumours and their metastases to the brain, spleen and thoracic lymph nodes, as established by the autopsy, chemotherapy would probably not have influenced survival, but certainly would have impaired the patient's quality of life. The patient decided on "wait and see" management and lived at home to the age of 80, thus saving the physicians the dilemma of performing invasive investigation and staging of the tumours. Considering that at the time of first admittance a lack of the possibility of effective therapy was already evident, even the objection to bronchoscopy could be considered reasonable.

In conclusion, in the case of synchronous triple cancers in an elderly patient the possibilities of effective therapy are limited. Therefore, invasive diagnostics and accurate staging may not be indicated in patients with bilateral advanced primary lung tumours. A "wait and see" decision can be quite a reasonable option.

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case report

Adenocarcinoma of the small bowel

Metka Šavli, Breda Jamar

Institute of Clinical Radiology, University Medical Centre, Ljubljana, Slovenia

Background. *Adenocarcinoma of small bowel is generally a rather rare primary tumour of small bowel with a prevalence rate of 0.5 – 3.0 / 100.000 population, but the most frequent tumour of small intestine. It more often involves the duodenum and jejunum than the ileum. The aim of this paper is also to point out the value of small bowel follow through (SBFT) in the diagnosis of stenosing lesions.*

Case report. *An 83 – year old male patient suffered from abdominal pain, malaise, vomiting, cachexia and diarrhoea for 3 months. The result of occult blood testing was negative. Haemoglobin level was normal. Proctoscopy, colonoscopy, upper gastrointestinal (GI) endoscopy, and ultrasonography (US) did not explain the patient's problems. Ileus of the small bowel was established with abdominal plain film. Small bowel follow through (SBFT) and computer tomography (CT) showed a stenosing tumour in the jejunum. Adenocarcinoma of the small bowel was established with histological examination after resection of the tumor.*

Conclusions. *SBFT, with manual compression of all segments of the small bowel, can be a very accurate diagnostic investigation for evaluation of stenosing lesions in this part of the intestine.*

Key words: intestinal obstruction; jejunal neoplasms; adenocarcinoma - radiography

Introduction

Comprising about 2 % of all gastrointestinal malignancies, malignant tumors of the small bowel are relatively rare [1], adenocarcinomas being the most frequent among them. Their peak incidence, slightly higher in males than in females, is in the 7 th decade.[2] More often they are found in the jejunum or duodenum. In the jejunum, adenocarcinomas are usually located within the first 30 cm distally of the ligament of Treitz.[3] Lymphatic spread to the regional lymph nodes and through the portal system to the liver are frequent. Peritoneal metastases can also be found, or there may be direct progression of the tumor into the adjoining structures.[4] Adult coeliac disease, Crohn's disease and Peutz – Jeghers syndrome are precancerous conditions.[5-7]

More specific symptoms are preceded by a period of vague abdominal discomfort, dyspepsia and malaise, often not alarming enough for the patient to seek medical advice. The more specific clinical presentation is associated with obstruction and ulceration of the cancer. Since the small bowel contents are liquid, obstructive symptoms

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Correspondence to: Breda Jamar MD, Institute of Clinical Radiology, University Medical Centre, Zaloška 7, SI-1000 Ljubljana, Slovenia. Tel. +386 1 522 8530; Fax: +386 1 522 2497; E-mail: breda.jamar@kclj.si

are somewhat late and may diminish to conservative treatment.

Because of its anatomy, small bowel is difficult to examine. The proximal jejunum and terminal ileum can be examined with enteroscopy, while for the stenosing processes in the mesenteric small intestine, radiologic examinations, especially dedicated SBFT and CT, are dominant diagnostic procedures.[8,9] On SBFT, the typical image of primary adenocarcinoma of the small intestine is an annular lesion of the » apple core » type.[2] It is usually symmetric, with a centrally positioned stricture. It is rigid and its shape is not significantly changed during compression of the abdomen.[10]

Case report

An 83-year-old man with arterial hypertension was first referred to the proctologist because of difficult defecation, abdominal pain and diarrhoea lasting for about one month. On proctoscopy, polyp of 5 – times 5 mm was found in the rectum. It was resected at a later colonoscopy and sent for histological examination. Some diverticula were also observed. With the upper GI endoscopy signs of chronic atrophic gastritis were found. With abdominal ultrasonography small cysts in the right kidney were revealed. However, the results of all examinations could not explain the patient's problems. Two months later the patient returned to the emergency department, for the third time in one month, because of severe vomiting and weight loss. Haemoglobin level was found normal. Dilated small bowel was observed on abdominal plain film (Figure 1), while no signs of acute abdomen were seen on physical examination, leading abdominal surgeons at the first two patient's visits to conclusion that there was no indication for surgery. At the third patient's visit to the emergency department, the gastroenterologist referred him to SBFT.

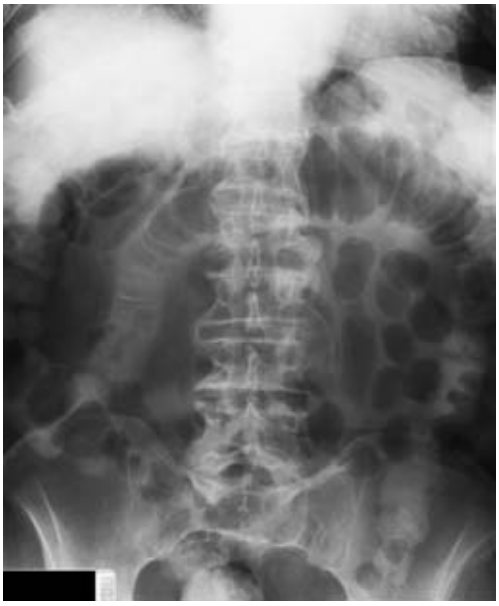


Figure 1. Abdominal plain film: dilated small bowel loops – obstruction.

On SBFT, the jejunum was found dilated, and an oval formation, approximately 3 – times 3 cm in size in the distal jejunum, causing relative obstruction, was revealed. Proximally to the formation, in a length of about 30 cm, thickened mucosal folds and irregular bowel wall were seen (Figure 2). The shape of the segment did not significantly change during compression of the abdomen. The process was obviously malignant, not inflammatory. As definite diagnosis could not be established, CT scan of the abdomen was done. It showed a solid tumour in the jejunum, 3 – times 3 cm in size (Figure 3, 4). There were no signs of spread into adjacent mesenteric fat. Radiologic signs of mechanical obstruction (dilated small bowel) could still be seen. No lymphadenopathy was found. With the exception of right cystic kidney, parenchymal organs were normal. There was some free fluid in the Proust's pouch.

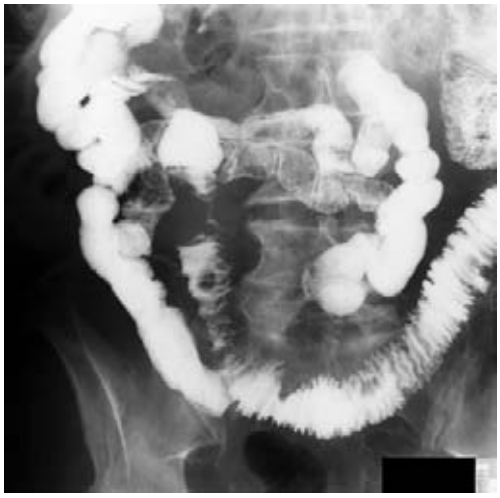


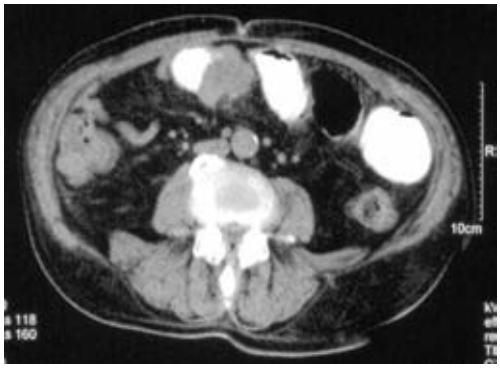
Figure 2. SBFT: Stenosis and an oval formation in the distal jejunum, causing a relative obstruction, thickened mucosal folds and irregular bowel wall proximally .

The patient was admitted to surgery. Implantation of pace maker for his arrhythmia was needed before he could be operated upon (5 days later). A 30 cm long segment of the jejunum was resected. Appendectomy was also performed. The histopathologic diagnosis was adenocarcinoma of the small bowel. One out of 17 nodes in the mesentery was found malignant. Lymphangiocarcinomatosis of the mesentery was also established.

Discussion

The performed examinations of the proximal and distal part of the alimentary tract – proctoscopy, colonoscopy, upper GI endoscopy – could not explain the patient's problems. Abdominal US revealed small cysts in the right kidney. The small bowel and colon attracted no attention of the ultrasonographist. It should be born in mind, however, that the interpretation of the bowel US is highly operator – dependent. Vast experience is needed to achieve accuracy rates comparable with those from the literature.[6]

On the three patient's visits of the emergency department in just one month because of the clinical progression of his state (severe vomiting, abdominal pain and loss of weight), signs of the small bowel mechanical ileus could be demonstrated with plain film of the abdomen, while no signs of acute abdomen could be seen on physical examination. The levels of haemoglobin were normal.



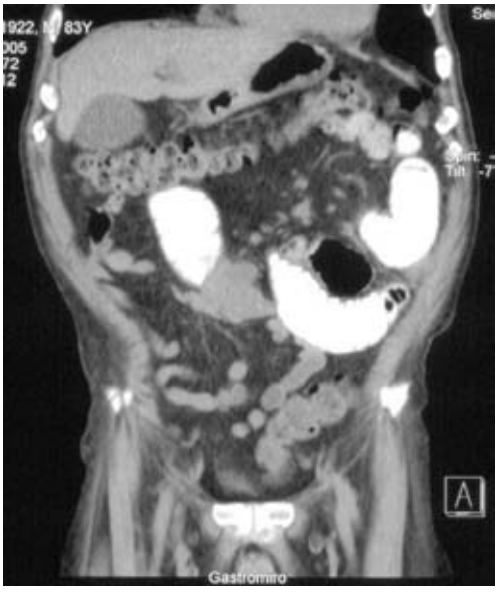


Figure 3 and 4. Computed tomography: A solid tumour in the jejunum. Dilated small bowel loops proximally.

In order to examine the mesenteric small bowel, a dedicated investigation, the SBFT, was indicated. The revealed oval formation, approximately 3 – times 3 cm in size, in the distal part of the jejunum, causing relative obstruction and thickened mucosal folds as well as irregular bowel wall proximally to the obstruction not changing during abdominal compression, could be recognised as malignant. As the changes were not typical of the small bowel adenocarcinoma, CT scan of the abdomen was performed for the differential diagnosis of lymphoma.

CT disclosed a solid tumour in the jejunum causing a relative obstruction and, proximally, dilatation of a small bowel loop. There was some free fluid in the pouch of Proust, but no signs of distal spread. The question whether it was a primary tumour or a direct progression from surroundings could not be answered.

Because of the radiologic signs of obstructive ileus, the results of SBFT and CT, the patent was admitted for surgery. A 30 cm long segment of the jejunum was resected. Appendectomy was also performed. The final diagnosis of adenocarcinoma of the small bowel was established with histopathologic examination.

Conclusion

Abdominal pain, vomiting, anaemia, and the presence of dilated proximal jejunum should suggest an obstructing neoplasm of the small bowel in older patients, and indicate the need for further diagnostic procedure with fluoroscopic small bowel study. The demonstration of a small bowel stenosing lesion depends primarily on SBFT. In most cases, the differentiation between malign or benign (e.g. inflammatory) lesion can be made, although the final diagnosis of the type of malignancy is done by histopathology.

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Functional form comparison between the population and the individual Poisson based TCP models

Colleen Schinkel[1,2], Nadia Stavreva[2], Pavel Stavrev[2], Marco Carlone[2,3] and B. Gino Fallone[1-3]

[1] Department of Physics, University of Alberta, [2] Department of Medical Physics, Cross Cancer Institute; [3] Department of Oncology, University of Alberta, Edmonton, Alberta, Canada

In this work, the functional form similarity between the individual and fundamental population TCP models is investigated. Using the fact that both models can be expressed in terms of the geometric parameters γ_{50} and D_{50}, we show that they have almost identical functional form for values of $\gamma_{50} \geq 1$. The conceptual inadequacy of applying an individual model to clinical data is also discussed. A general individual response TCP expression is given, parameterized by D_f and γ_f – the dose corresponding to a control level of f, and the normalized slope at that point. It is shown that the dose-response may be interpreted as an individual response only if γ_{50} is sufficiently high. Based on the functional form equivalency between the individual and the population TCP models, we discuss the possibility of applying the individual TCP model for the case of heterogeneous irradiations. Due to the fact that the fundamental population TCP model is derived for homogeneous irradiations only, we propose the use of the EUD, given by the generalized mean dose, when the fundamental population TCP model is used to fit clinical data.

Key words: radiotherapy dosage; Poisson distribution; dose-response relationship, models, statistical, TCP

Introduction

In the decades following the introduction of the first individual TCP model by Munro and Gilbert,[1] the distinction between the individual and population response has often been disregarded and individual TCP models have been fit to clinical datasets. The necessity of describing the impact of population heterogeneity on dose-response has lead to the development, by a number of authors, of population-based tumour control probability (TCP) models.[2-5]

It has been shown that the presence of population heterogeneity leads to a dose-response curve that is flattened relative to the individual dose-response curve. If an individual TCP model is fit to a population dataset, the biological meaning of the parameter estimates is lost – the radiobiological parameters take on unrealistically low values.[6] Nevertheless, although it is conceptually incorrect, the individual TCP model has been fit to clinical datasets and

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Correspondence to: B. Gino Fallone, Ph.D., Department of Medical Physics, Cross Cancer Institute, 11560 University Ave., Edmonton, Alberta, T6G 1Z2, Canada. Tel: (780) 432-8750, Fax: (780) 432-8615; E-mail: ginofall@cancerboard.ab.ca,

parameters obtained from these fits have been assumed to have radiobiologically meaningful values.[4,7-10] On the other hand, it has also been shown that these fits are characterized by an acceptable goodness of fit.

It has been expected that the population TCP models would allow for the estimation of biologically meaningful population parameters. Unfortunately, it is impossible to obtain a unique set of parameter values when a population TCP model is fit to clinical data.[6,11] This is due to the fact that different sets of population parameter values produce almost identical TCP curves. Carlone *et al*.[11] analytically demonstrated that when the dominant source of inter-patient heterogeneity is that of tumour radiosensitivity, the population TCP function has only two independent parameters – the dose at 50% TCP, D_{50}, which determines the position of the TCP curve, and the normalized slope of the curve, γ_{50}. These parameters have geometric meaning. Since it is also true that the individual TCP model may be expressed in terms of the same two parameters,[3,12] it is possible that, for a given range of parameter values, both models will exhibit almost identical functional form. In this work, we investigate the similarities between these two models expressed in terms of D_{50} and γ_{50} by plotting them for identical values of these geometric parameters.

Background and method

The general form of the population-based Poisson TCP model has eight parameters. However, it has previously been shown[6,11] that the parameters of such a model are interrelated; many different combinations of parameters lead to one and the same TCP curve. Thus, it may seem difficult to directly compare the functional forms of the individual and population-based TCP models. On the other hand, Carlone *et al*.[11] have specified (based on a certain approximation, of course, but a clinically valid one) what these interrelations actually are, and have shown that there are only two independent population model parameters – D_{50} and γ_{50}. Fortunately, the individual Pooison-based TCP module can also be parameterized by these parameters. This fact makes the comparison of both models an easier task.

The Poisson-based individual TCP model

This common form of the individual TCP model is based on Poisson statistics combined with a simplified description of clonogen repopulation.[4,10,11,13-26] In the case where a tumour undergoes homogeneous irradiation to a total dose D, split into n fractions with equal dose per fraction, d, the individual Poisson TCP model may be written as:[11]

$$[1] \qquad TCP_{ind} = e^{-N_S} = \exp\left[-N_0 e^{-(\alpha+\beta d)D+\lambda T}\right] = \exp\left[-N_0 e^{-\left(\alpha+\beta d-\frac{\lambda'}{d}\right)D}\right] = \exp\left[-N_0 \exp\left(-\alpha' D\right)\right],$$

where N_0 is the initial number of clonogens, N_S is the mean number of clonogens surviving the treatment, α and β are the linear quadratic (LQ) radiosensitivity parameters, λ is the tumour repopulation rate, T is the total treatment time and $\lambda' = \lambda(T/n)$. Note that as long as an equal dose is given during each fraction of the treatment (which is common clinical practice), the parameters α, β and λ' can be combined into one single parameter:

[2] $$\alpha' = \alpha + \beta d - \frac{\lambda'}{d}.$$

The validity of the Poisson TCP model was questioned by Tucker and Travis,[21] and others[27-31] who explored the non-Poisson nature of the TCP in the case where tumour repopulation occurs. Under certain conditions, however, it has been shown[27,32] that the distribution of the number of clonogen cells remaining at the end of a treatment is well-approximated by the Poisson distribution. In view of these results, and also because of the relative complexity of the non-Poissonian TCP models, the individual TCP function presented in Eq. [1] is often used.

A form of the individual TCP model[3,12] that is equivalent to Eq. [1], but written in terms of the geometric parameters, γ_{50} and D_{50}, is given by:

[3a] $$TCP_{ind} = 0.5^{\exp\left[\frac{2\gamma_{50}}{\ln 2}\left(1-\frac{D}{D_{50}}\right)\right]}.$$

The notion of normalized slope, γ, was first introduced by Brahme[33] for the purpose of dosimetric precision quantification. Later, Kallman *et al*.[34] used the maximum value of γ at the inflection point of the TCP curve and derived an expression similar to Eq. [3a], but as pointed out by Bentzen and Tucker,[35] a slight inconsistency is present in their formula. In general, the Poisson TCP expression given by Eq. [1], may be transformed and parameterized in terms of the normalized slope γ_f at any dose point D_f:

[3b] $$TCP_{ind} = f^{\exp\left[\frac{-\gamma_f}{f\ln f}\left(1-\frac{D}{D_f}\right)\right]}$$

From Eqs. [1] and [3b], the following relationships between the two different sets of parameters (γ_f, D_f) and (N_0, α') may be derived:

[4a] $$D_f = \frac{1}{\alpha'}\ln\left(\frac{-N_0}{\ln f}\right)$$

[4b] $$\gamma_f = -f\ln f\ln\left(\frac{-N_0}{\ln f}\right). \quad .$$

and for (γ_{50}, D_{50}) in particular:

[5a] $$D_{50} = \frac{1}{\alpha'}\ln\left(\frac{N_0}{\ln 2}\right)$$

[5b] $$\gamma_{50} = \frac{\ln 2}{2}\ln\left(\frac{N_0}{\ln 2}\right). \quad .$$

The population-based TCP model

Carlone *et al*.[11] showed that the population TCP model for the case of dominant heterogeneity in radiosensitivity may be written as:

[6] $$TCP_{pop} = \frac{1}{2}erfc\left[\sqrt{\pi}\,\gamma_{50}\left(\frac{D_{50}}{D}-1\right)\right].$$

The parameters in Eq. [6] – D_{50} and γ_{50} – have the same geometric meaning as the corresponding parameters in Eq. [3a]. The geometric parameters may be expressed in terms of the population-based radiobiological parameters, $\overline{\alpha'}$, σ' and $\overline{\ln N_0}$:[11]

[7a] $$D_{50} = \frac{\Gamma + \ln N_0}{\overline{\alpha'}}$$

[7b] $$\gamma_{50} = \frac{\overline{\alpha'}}{\sqrt{2\pi}\sigma'}$$

Here $\overline{\alpha'} = \overline{\alpha} + \overline{\beta} d + \frac{\overline{\lambda'}}{d}$ and $(\sigma')^2 = \sigma_\alpha{}^2 + d^2\sigma_\beta{}^2 + \frac{\sigma_{\lambda'}{}^2}{d^2}$ where $\overline{\alpha}$, $\overline{\beta}$, $\overline{\lambda'}$ and $\overline{\ln N_0}$ are the population averages of the corresponding individual parameters and σ_α, σ_β, $\sigma_{\lambda'}$ and $\sigma_{\ln N_0}$ are their standard deviations. The symbol Γ represents Euler's gamma constant, which has an approximate value of 0.577.

The general form of the Carlone *et al.*[11] population TCP model takes both heterogeneity in radiosensitivity and heterogeneity in clonogen number into account. However, this form of the population TCP model has three parameters, and was shown[11] to be almost identical to the one that only takes heterogeneity in radiosensitivity into account. Hence, the latter will be used for this analysis.

Functional form comparison between individual and population-based TCP models

Since both the individual and the population TCP models may be written in terms of the same two parameters, γ_{50} and D_{50}, it seems natural to assume that the two models may display similarity in functional form. In order to explore the functional similarity of these models, Eqs. [3a] and [6] are evaluated for a given range of γ_{50} and D_{50} values. Subsequently, the individual and population TCP curves obtained for equal sets of γ_{50} and D_{50} values are plotted for visual comparison.

The functional closeness of the individual and the population TCP curves may be more rigorously estimated by calculating the normalized difference between the areas under the two TCP curves,

[8] $$\frac{\Delta A}{A_{TCP_{pop}}}(\gamma_{50}) = \frac{\left(A_{TCP_{pop}} - A_{TCP_{ind}}\right)}{A_{TCP_{pop}}},$$

as a function of γ_{50}.

Results

The individual and the population TCP curves were calculated according to Eqs. [3a] and [6] for values of the parameters γ_{50} and D_{50} reported by Okunieff *et al.*[36] Based on their estimates of γ_{50}, we chose a range of $\gamma_{50} \in [0.5, 6]$. These authors also reported a mean D_{50} for all tumours investigated in their work of 50 Gy, with values ranging from 10 to 90 Gy. We therefore chose a value of D_{50} = 50 Gy for our investigation.

Figure 1 shows eight pairs of individual and population TCP curves calculated for the following parameter values: D_{50} = 50 Gy and γ_{50} = [0.5, 1, 1.5, 2, 2.5, 3, 4, 6]. This figure was reproduced for different values of D_{50}, to determine whether this parameter

had any influence on functional equivalency. It was found that the location of the TCP curves along the dose-axis did not influence the shapes of the curves or their positions relative to each other. Hence, the results shown in Figure 1 are applicable for any D_{50} value.

The quantity $\frac{\Delta A}{A_{TCP_{pop}}}(\gamma_{50})$ (Eq. [8]) is plotted in Fig. 2. The largest area difference between the two TCP curves is -17.7% obtained at $\gamma_{50} = 0.5$.

Discussion

Based on Figures 1(d) – 1(h) and Figure 2, one may conclude that the functional forms of the individual and the population models are almost identical for $\gamma_{50} \in [2, 6]$. Indeed, for this range of γ_{50} the index $\left|\Delta A / A_{TCP_{pop}}\right|$ is less than 0.5%. Although $\left|\Delta A / A_{TCP_{pop}}\right|$ is higher ($\Delta A / A_{TCP_{pop}} \in [-0.5, -6.7]\%$) for the interval $\gamma_{50} \in [1, 2)$, the plots in Figures 1(b) and 1(c) indicate that the individual and population TCP curves are still sufficiently close to each other, especially for the clinically-relevant high dose range. The individual and population models differ considerably at $\gamma_{50} = 0.5$ ($\left|\Delta A / A_{TCP_{pop}}\right| = 17.7\%$). As can be seen from Figure 1, for γ_{50} less than 2.5 the individual curves overread TCP everywhere except at 50% control when compared with the population-based TCP curves. For normalized slopes above γ_{50} = 2.5, the individual curves tend to slightly underread the population TCP. The overreading and underreading tendencies are clearly demonstrated by Figure 2.

The considerable closeness in functional form of both models explains the observation that the individual TCP model produces a reasonable fit to clinical datasets.[4,10] In spite of this, the observed equivalence in functional form of the two TCP models should not be regarded as an endorsement to use the individual TCP model to fit clinical data.

However, a very steep dose response is unusual for clinical data sets. Shallower responses are much more typical for populations of patients. Therefore, it would conceptually be more correct to use the population TCP model, which accounts for inter-patient heterogeneity to fit such data. If, however, the individual TCP model is used, one should bear in mind that the obtained parameter values have lost their biological meaning and should be interpreted simply as phenomenological coefficients.

As can be seen from Figures 1(a) and 1(b), both models start to differ in functional form for the clinically observable range of $\gamma_{50} < 1$. In addition, for these values of γ_{50}, the individual model leads to TCP > 0 for D = 0. Therefore, fits to very shallow curves using the individual model may distort the best-fit estimates of γ_{50} and D_{50}.

The authors advocate the use of the population model in regards to clinical data. However, the demonstrated equivalence in functional form of the individual and population models can be utilized for the case of heterogeneous tumour irradiation. In this case, the individual TCP model with existing $\{\gamma_{50}, D_{50}\}$ estimates (e.g. Okunieff *et al.*[36]) can be used for the evaluation of TCP[37] according to the following expression:[38]

$$[9] \qquad TCP = 0.5^{\sum_i v_i \exp\left[\frac{2\gamma_{50}}{\ln 2}\left(1-\frac{D_i}{D_{50}}\right)\right]}$$

Equation [9] is a simple, straightforward generalization of Eq. [3] for the case of heterogeneous irradiation. The generalization of Eq. [6] for the case of heterogeneous irradiation, without introducing extra model pa-

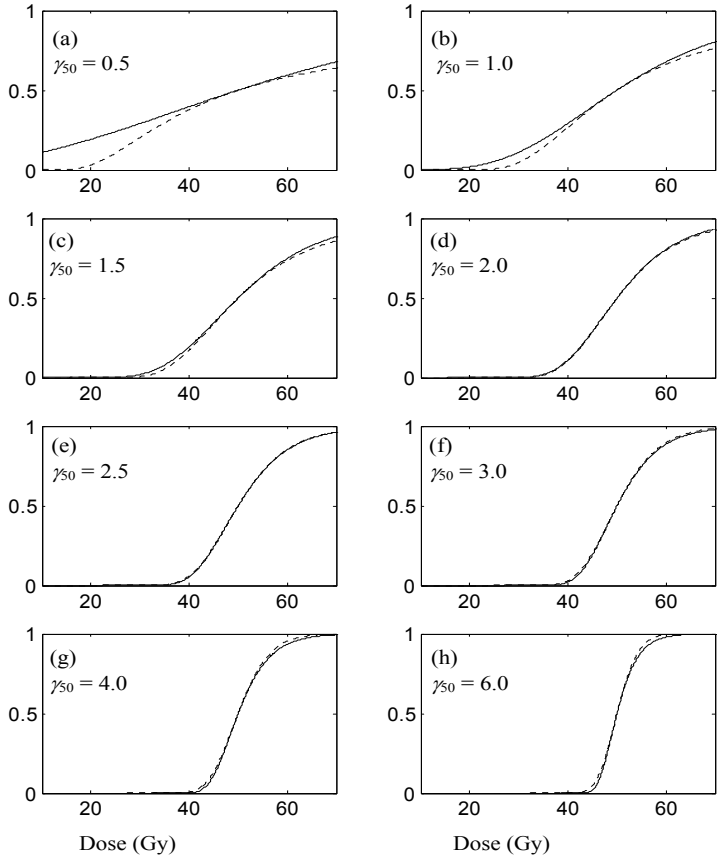

Figure 1. Individual (solid) and population-averaged (dotted) TCP curves for D_{50} = 50 Gy and the γ_{50} values shown in each sub-plot.

rameters, presents a complicated mathematical problem, and has not yet been solved.

Strictly speaking, the ability to use Eq. [9] as a population TCP descriptor has not yet been proven theoretically. Nevertheless, our experience with the TCP/NTCP estimation module[37] shows that it produces reasonable TCP estimates.

Another approach to the problem of taking dose heterogeneity into account for the population TCP model is to replace the homogeneous dose, *D*, with the equivalent uniform dose, EUD. It may then be assumed that the EUD is equal to the generalized mean dose (GMD), as is usually done.[39,40] Unfortunately, this approach introduces a third model parameter, and knowledge of its value for each tumour type would then be needed in order to use this model to calculate TCP for a heterogeneously irradiated tumour. Therefore, until more comprehensive parameter estimates are produced through fits of the population TCP model to clinical data for the case of heterogeneous irradiation, we propose that Eq. [9] be used for evaluation of treatment plans in terms of TCP, based on the functional form equivalency of both models.

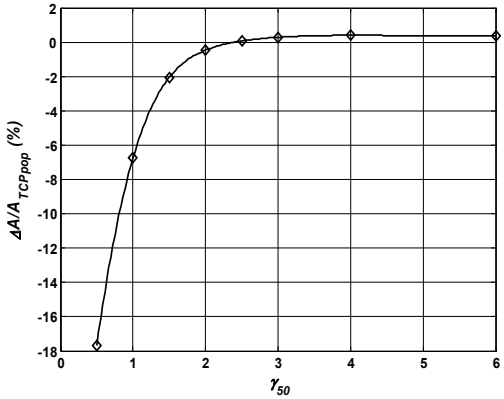

Figure 2. The ratio of the area difference, $\Delta A = A_{TCPpop} - A_{TCPind}$, between the two TCP curves, to the total area under the population TCP curve (A_{TCPpop}), plotted for the values of γ_{50} used to generate the curves shown in Figure 1.

Conclusions

It is thus concluded that:

- The population and the individual TCP responses are almost identical in functional form for γ_{50} belonging to the interval [1, 6]. If each of these models were fit to the same clinical dataset, they would produce statistically indistinguishable values of the parameters D_{50} and γ_{50}.
- It is conceptually incorrect to use the individual TCP model to fit clinical data.
- Until reliable estimates of the population TCP parameters for the case of heterogeneous tumour irradiation are obtained, the individual TCP model (Eq. [9]) with existing D_{50} and γ_{50} estimates could be used for TCP evaluations in this situation.
- The case of a shallow dose-response relationship, which is usually observed clinically, can be explained by the presence of significant inter-patient heterogeneity. The population TCP model should be used to fit such data, as it accounts for this heterogeneity. If, however, the individual TCP model is used, the estimated parameter values should be interpreted simply as phenomenological coefficients.
- A steep dose-response relationship indicates the presence of a relatively small inter-patient heterogeneity. Though it is highly improbable to observe such dose-responses clinically, the individual TCP model may be applied to such data for the purpose of estimating biological parameters, as the individual parameters would retain some biological meaning in this case.

Acknowledgements

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Radiol Oncol 2007; 41(2): 57-62.

Mediastinitis in empiem plevre zaradi širjenja zobnega vnetja

Juretic M, Belusic-Gobic M, Kukuljan M, Cerovic R, Golubovic V, Gobic D

Izhodišča. Zobna vnetja so pogosta, vendar se redko širijo v vrat in v podorčje prsnega koša. Akutni gnojni mediastinitis (spuščajoči se nekrozantni mediastinitis) je bolezen, ki ima kljub zdravljenju z antibiotiki in kirurškim posegom do 40% smrtni izhod. Izjemno redko se kot posledica mediastinitsa razvije plevralni empiem.

Prikaz primera. Prikazan je primer mladega, predhodno zdravega bolnika z mediastinitisom in obojestranskim plevralnim empiemom, ki je nastal kot posledica širjenja zobnega vnetja. V začetku je bil zdravljen s kirurškima posegoma na vratu. Po CT preiskavi prsnega koša, ki je pokazala širjenje vnetja v prsni koš, je bila narejena torakotomija in drenaža obojestranskega empiema plevre z antibiotskim zdravljenjem. Bolnik je ozdravel, kljub zakasnelem spoznanju zapleta zobnega vnetja.

Zaključki. Pri zgodnji diagnostiki spuščajočega se nekrotizantnega mediastinitisa, ki nastane zaradi zobnega vnetja, je CT preiskava prsnega koša pomembna diagnostična metoda saj omogoča ustrezno zdravljenje bolnika.

Radiol Oncol 2007; 41(2): 64-71.

Rak ledvic

Rajer M

Izhodišča. Namen prispevka je prikazati trenutno stanje na področju diagnostike in zdravljenja raka ledvic (RL), s poudarkom na slovenskih epidemioloških podatkih. Rak ledvic predstavlja 2% vseh rakov in je tretji najpogostejši rak genitourinarnega področja. V veliki večini prizadene ljudi med 50 in 60 letom starosti. Pogostejši je pri moških kakor pri ženskah. Z nastankom RL naj bi bili povezani številni dejavniki tveganja. Še najmočneje je dokazana povezava s kajenjem tobaka. Ostali pomembni dejavniki tveganja so še hipertenzija, debelost in kronična ledvična odpoved. V polovici primerov pridejo bolniki na prvi pregled k zdravniku, ko je bolezen že napredovala, saj RL pogosto ne spremljajo značilni simptomi. RL najpogosteje metastazira v pljuča (75%), nato v mehka tkiva (36%), kosti (20%), jetra (18%), kožo (8%) in centralni živčni sistem (8%). V diagnostiki prevladujejo slikovne metode.

Zaključki. Lokalizirano bolezen zdravimo kirurško z radikalno nefrektomijo. Ohranitvena operacija je indicirana, ko bi odstranitev celotne ledvice privedla bolnika do dialize. Do danes še ni bila odkrita učinkovita dopolnilna terapija po operaciji. Metastatsko bolezen zdravimo z interferonom in interlevkinom, prihajajo pa vedno nova in učinkovitejša biološka zdravila. Najpomembnejši prognostični dejavnik za preživetje je stadij bolezni ob začetku zdravljenja. Petletno preživetje bolnikov z RL je 95% za stadij I, 88% za stadij II, 59% za stadij III in 20% za stadij IV.

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Prikaz primera z Mayo Clinic: Lokalno napredovali karcinom Bartholinijeve žleze

Pinn ME, Austin LM, Schomas DA, Miller RC

Tumorji Bertholinijeve žleze so redki, predstavljajo manj kot 5% malignomov vulve. Zdravljenje poteka v največji meri po načelih za zdravljenje karcinomov vulve ali analnega kanala. Predstavljen je primer invazivnega, slabo diferenciranega skvamoznega karcinoma Bartholinijeve žleze. V anamnezi 47. letne bolnice izstopa predhodna cervikalna intraepitelijska neoplazija, zdravljen s konizacijo, sladkorna bolezen tipa 2, in kajenje. Zdravljena je bila s predoperativno radioterapijo v kombinaciji s 5-fluorouracilom in cisplatinom, čemur je sledila ponovna ocena razširjenosti bolezni ter operacija z rekonstrukcijo vagine.

Radiol Oncol 2007; 41(2): 80-5.

Trojni sočasni rak: medicinski in etični problem

Debevec L, Cesar R, Kern I

Izhodišča. Pri bolniku, pri katerem sumimo na sočasni rak, so možnosti za učinkovito zdravljenje omejene. Zato se postavlja vprašanje invazivne diagnostike in natančne zamejitve, posebno pri starejših bolnikih s slabo telesno zmogljivostjo, ki so primerni le za simptomatsko zdravljenje.

Opis primera. 78-letni bolnik z arterijsko hipertenzijo in angino pektoris je bil sprejet v bolnišnico zaradi sinkope. S slikovnimi preiskavami smo ugotovili dva primarna tumorja pljuč in tumor ledvice. Bolnik je odklonil invazivno diagnostiko in po nekaj dneh smo ga odpustili domov. 19 mesecev kasneje je bil ponovno sprejet v slabem kliničnem stanju in je umrl zaradi pljučnice. Avtopsija je pokazala: ploščatocelični rak desnega zgornjega pljučnega režnja z zasevki v regionalne bezgavke in možgane, drobnocelični rak levega zgornjega pljučnega režnja z zasevki v regionalne bezgavke in vranico ter svetlocelični rak desne ledvice s številnimi zasevki v obeh pljučnih krilih. Vsi tumorji so bili nekrotični. Zaradi tega sklepamo, da poskus specifičnega zdravljenja verjetno ne bi bil uspešen.

Zaključki. Pri starejšem bolniku z napredovalim pljučnim rakom, pri katerem sumimo na trojni sočasni rak, je lahko najbolj ustrezna odločitev spremljanje bolnika.

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Adenokarcinom ozkega črevesa

Šavli M, Jamar B

Izhodišča. Adenokarcinom ozkega črevesa je redko maligno obolenje, s prevalenco 0.5-3.0/100.000. Pogosteje prizadene dvanajstnik in jejunum kot ileum.
Prikaz primera. 83 letni moški je imel bolečine v trebuhu 3 mesece. Navajal je slabo počutje, bruhanje in driske, bil je kahektičen. Krvne preiskave so bile v mejah normalnih. Izvidi koloskopije, gastrokopije in ultrazvočnega pregleda so bili prav tako še v mejah normalnih. Pri dvakratnem pregledu v urgentnem bloku abdominalni kirurg ni odkril znakov za akutno kirirurško oboblenje. Pri obeh pregledih so bile na rentgenskem posnetku trebuha vidna razširjene vijuge ozkega črevesa, rentgenski znak ileusa. Ob tretjem pregledu v urgentnem bloku je intrenist napotil bolnika na rentgenski pregled ozkega črevesa, kjer je bila opažena stenozantna sprememba v jejunumu, po videzu maligna. Bolnik je opravil še računalniško tomografijo trebuha. Pri operaciji so resecirali 30 cm jejunuma, histološko je bil dokazan adenokarcinom.
Zaključek. Jejunoileografija je zanesljiva diagnostična metoda za prikaz stenozantnih sprememb ozkega črevesa, v večini primerov tudi za razlikovanje med benignimi in malignimi spremembami.

Radiol Oncol 2007; 41(2): 90-8.

Primerjava Poissonovih TCP modelov za posameznika in populacijo

Schinkel C, Stavreva N, Stavrev P, Carlone M, Fallone BG

Raziskali smo podobnost TCP modelov za posameznika in populacijo. Z ozirom na to, da lahko oba modela opišemo z geometrijskima parametroma γ_{50} in D_{50}, smo pokazali, da dobita skoraj enako obliko pri vrednostih $\gamma_{50} \geq 1$. Obravnavali smo neprimernost uporabe modela za posameznika na kliničnih podatkih. Podali smo splošen izraz za TCP in ga parametrizirali z D_f in γ_f – z dozo, kjer TCP zavzame vrednost f in z normaliziranim naklonom v tej točki. Izkazalo se je, da lahko krivuljo interpretiramo kot odziv posameznika le ob dovolj velikem γ_{50}. Na osnovi podobnosti TCP modelov za posameznika in populacijo smo obravnavali možnost uporabe slednjega v primeru neenakomernega obsevanja. Ker osnovni TCP model za populacijo predpostavlja enakomerno obsevanje, smo predlagali, da se pri uporabi na kliničnih podatkih vrednost parametra EUD izenači s povprečno dozo.

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July 5-8, 2007
The "ESMO Conference Lugano" will take place in Lugano, Switzerland.
Contact ESMO Head Office, Congress Department, Via La Santa 7, CH-6962 Viganello-Lugano, Switzerland; or +41 (0)91 973 19 19; or fax +41 (0)91 973 19 18; or e-mail congress@esmo.org; or see http://www.esmo.org/activities/ecluconference/

Radiotherapy

July 1-5, 2007
The ESTRO teaching course "IMRT and Other Conformal Techniques in Practice" will take place in Vienna, Austria.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Radiation oncology

July 1-6, 2007
The ESTRO teaching course "Evidence Based Radiation Oncology: Methodological Basis & Clinical Application (extra edition)" will take place in Krakow, Poland.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Toxicology

July 15-19, 2007
The "11th International Congress of Toxicology" will be offered in Montreal, Canada.
Contact Congress Secretariat, e-mail: ict2007@nrc-cnrc.gc.ca; or see http://www.ict2007.org

Radiotherapy

August 22-25, 2007
The ESTRO teaching course "3D Planning and Imaging (special edition)" will take place in St Petersburg, Russia.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Gynaecology

August 30 – September 1, 2007
The ESTRO teaching course "3D Image-based Brachytherapy in Gynaecological Malignancies" will take place in Copenhagen, Denmark.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Lung cancer

September 2-6, 2007
The "12th World Conference on Lung Cancer" will be offered in Seoul, Korea.
Contact Conference Secretariat; e-mail WCLC2007@ncc.re.kr; or see http://www.iaslc.orgIumages/12worldconfannounce.pdf

Oncology

September 7, 2007
The EORTC annual course "One-Day Introduction to EORTC Trials" will take place in Brussels, Belgium.
Contact Mr. Danielle Zimmermann; EORTC Education Office, Avenue E. Mounier, 83, bte 11, B-1200 Brussels, Belgium; or call +32 2 774 16 02; or fax +32 2 772 61 33; or e-mail Danielle.zimmermann@eortc.be; or see http://www.eortc.be

Radiotherapy

September 8-13, 2007
The "9th Biennial ESTRO Meeting on physics and Radiation Technology for Clinical Radiotherapy will take place in Barcelona, Spain.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Hematologic malignancies

September 14-15, 2007
The NCCN 2nd Annual Congress: "Hematologic Malignancies " will take place in New York, USA.
Contact National Comprehensive Cancer Network, 500 Old York Road, Suite 250 Jenkintown, PA 19046, USA; or call +1 215.690.0300; or fax +1 215.690.0280; or e-mail support@nccn.ecimail.net; or see http://www.nccn.org

Oncology

September 23-27, 2007
The "14th European Cancer Conference ECCO 15/ ESTRO 26" will take place in Barcelona, Spain.
Contact Conference Secretariat, ECCO 14, The European Cancer Conference, European Cancer Societies (FECS), Avenue E. Mounier, 83, B-1200 Brussels, Belgium; or call +32 2 775 02 01; or fax +32 2 775 02 00; or e-mail ECCO14@fecs.be; or see http://www.fecs.be

Radiotherapy

September 30 – October 4, 2007
The ESTRO teaching course "Radiotherapy with Protons and Ions" will take place in Heidelberg, Germany.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Radiobiology

October 14-18, 2007
The ESTRO teaching course "Basic Clinical radiobiology" will take place in Giardini Naxos, Italy.
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Radiotherapy

October21-25, 2007
The ESTRO teaching course "Physics for Clinical radiotherapy" will take place in Limassol, Cyprus.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Radiation oncology

November 11-16, 2007
The ESTRO teaching course "Evidence Based Radiation Oncology: Methodological Basis & Clinical Application" will take place in Athens, Greece.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Prostate cancer

November 15-17, 2007
The ESTRO multidisciplinary prostate cancer meeting will be offered.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Radiotherapy

December 9-13, 2007
The ESTRO teaching course "Image-Guided Radiotherapy in Clinical Practice" will take place in Brussels, Belgium.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Lung cancer

June 12-14, 2008
The "11th Central European Lung Cancer Conference" will be offered in Ljubljana, Slovenia.
Contact Conference secretariat, Ms. Ksenia Potocnik, Department of Thoracic Surgery, Medical Centre Ljubljana, Slovenia; or call +386 1 522 2485; or fax +386 1 522 3968; or e-mail ksenia.potocnik @kclj.si; or see http://en.ce-lung2008.org/

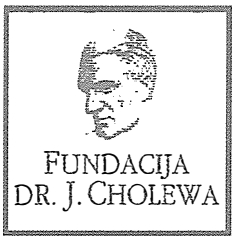
Lung cancer

August 21-24, 2009
The "13th World Conference on Lung Cancer" will be offered in San Francisco, USA.
Contact Conference Secretariat; e-mail WCLC2007@ncc.re.kr; or see http://www.iaslc.orgIumages/12worldconfannounce.pdf

Oncology

September 4-8, 2009
The "34th ESMO Congress" will take place in Vienna, Austria.
Contact ESMO Head Office, Congress Department, Via La Santa 7, CH-6962 Viganello-Lugano, Switzerland; or +41 (0)91 973 19 19; or fax +41 (0)91 973 19 18; or e-mail congress@esmo.org; or see http://www.esmo.org

As a service to our readers, notices of meetings or courses will be inserted free of charge.
Please send information to the Editorial office, Radiology and Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia.



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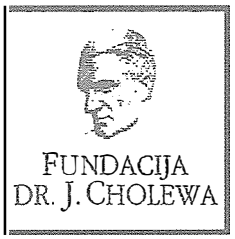

Activity of »Dr. J. Cholewa« Foundation for Cancer Research and Education – a report for the second quarter of 2007

The Dr. J. Cholewa Foundation for Cancer Research and Education plans to continue focusing its activities and attention to cancer research and education in Slovenia. In this setting, it plans to promote all the forms of cancer education in general population, among medical and nursing students and in general population. The Dr. J. Cholewa Foundation for Cancer Research and Education will also continue to deal carefully and with great attention with the requests and proposals for research grants and scholarships. The Foundation members with clinical and research experience in cancer and members with important experience in finance will continue to be instrumental in this activity.

The Dr. J. Cholewa Foundation for Cancer Research and Education continues to support the regular publication of "Radiology and Oncology" international medical scientific journal in 2007. This journal is edited, published and printed in Ljubljana, Slovenia. This support is in line with the philosophy of the Foundation, emphasizing the spread of information and knowledge among many professionals in clinical and laboratory cancer research in Slovenia, but it also gives special attention to many interested individuals in lay public and others in Slovenia and elsewhere. In addition, the Dr. J. Cholewa Foundation for Cancer Research and Education bestowed and allocated by a number research and study grants 2006 and will continue with this activity in 2007. The Foundation pays special attention to the support of the publication of the results from cancer research in Slovenia in respectable international scientific journal worldwide.

The Dr. J. Cholewa Foundation for Cancer Research and Education respectfully acknowledges the contribution of its members with clinical and research experience in cancer and its members with experience in finance. Without their efforts the Foundation would not be able to continue with its mission.

Borut Štabuc, MD, PhD
Tomaž Benulič, MD
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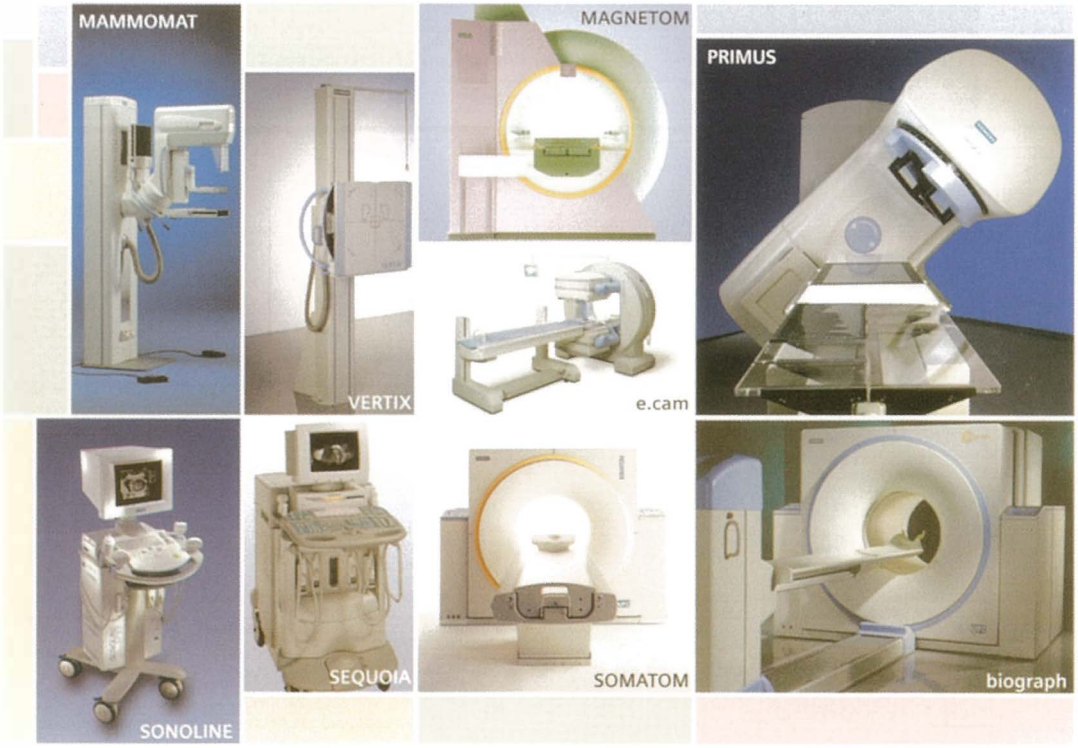

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topotekan

Hycamtin v kombinaciji s cisplatinom dokazano podaljša preživetje pri napredovalem raku materničnega vratu.[1]

Sestava HYCAMTIN 4 mg prašek za koncentrat za raztopino za infundiranje. Vsaka viala vsebuje 4 mg topotekana (v obliki klorida) **Indikacije** Samostojno zdravljenje s topotekanom je indicirano pri bolnicah z rakom jajčnika z metastazami, če terapija prve izbire in tudi naslednje terapije niso uspele; bolnikih z relapsom drobnoceličnega pljučnega raka, pri katerih ponovno zdravljenje s terapijo prve izbire ni primerno. Topotekan v kombinaciji s cisplatinom je indiciran pri bolnicah s ponovitvijo karcinoma materničnega vratu po zdravljenju z obsevanjem in bolnicah s stadijem IVB karcinoma materničnega vratu. **Odmerjanje in način uporabe** *Karcinom jajčnika in drobnocelični pljučni karcinom; Začetni odmerek* Priporočeni odmerek topotekana je 1,5 mg/m² telesne površine na dan, z intravensko infuzijo, ki traja po 30 minut dnevno, v ciklih po 5 zaporednih dni in s tritedenskimi presledki med začetki vsakega cikla zdravljenja. Čega bolniki dobro prenašajo, smemo z zdravljenjem nadaljevati, dokler je bolezen v progresiji. *Nadaljevalni odmerki* Pred naslednjo uporabo topotekana mora biti število nevtrofilcev 1 x 10^9/l, število trombocito v 100 x 10^9/l, vrednost hemoglobina pa 9 g/dl (po transfuziji, čeje le-ta potrebna).Bolnike s hudo nevtropenijo (število nevtrofilcev < 0,5 x 10^9/l), ki traja 7 ali več dni, ali hudo nevtropenijo z zvišano telesno temperaturo ali okužbo, ali tiste, ki jim je bilo treba zdravljenje preložiti zaradi nevtropenije, zdravimo tako, da uporabimo manjši odmerek, tj. 1,25 mg/m² na dan (ali ga po potrebi še dodatno zmanjšamo do 1,0 mg/m² na dan) ali dajemo v naslednjih ciklih profilaktično G-CSF za ohranjanje enake jakosti odmerka. Začnemo na 6. dan cikla (naslednji dan po prenehanju vnašanja topotekana). Če se nevtropenija z vnašanjem G-CSF ustrezno ne popravi, je odmerke treba zmanjšati. Podobno je treba zmanjšati odmerke, če pade število trombocitov pod 25 x 10^9/l. Med kliničnimi preskušanji so topotekan prenehali uporabljati, če je bil odmerek že zmanjšan na 1,0 mg/m² in bi ga bilo treba zaradi neželenih učinkov še dodatno zmanjšati. *Karcinom materničnega vratu; Začetni odmerek* Priporočen! odmerek topotekana je 0,75 mg/m²/dan. Bolnica ga 1., 2. in 3. dan prejme v obliki 30-minutne intravenske infuzije enkrat na dan. 1. dan po prejemu odmerka topotekana bolnica prejme še intravensko infuzijo cisplatina v odmerku 50 mg/m²/dan. Takšna shema zdravljenja se ponavlja vsakih 21 dni, 6 ciklov ali dokler je bolezen v progresiji. *Naslednji odmerki* Bolnica topotekana ne sme prejeti, če število nevtrofilcev ni večje ali enako 1,5 x 10^9/l, število trombocitov večje ali enako 100 x 10^9/l in vrednost hemoglobina večja ali enaka 9 g/dl (po transfuziji, če je le-ta potrebna). Pri bolnicah s febrilno nevtropenijo (število nevtrofilcev manjše od 1 x 10^9/l in telesna temperatura 38 °C ali večja) je pri naslednjih ciklih priporočljivo odmerek topotekana zmanjšati za 20 % na 0,60 mg/m²/dan.V primeru febrilne nevtropenije je alternativa zmanjšanju odmerka lahko dajanje G-CSF po naslednjem ciklu (pred zmanjšanjem odmerka). Z njim se začne 4. dan cikla (vsaj 24 ur po koncu dajanja topotekana).Če je febrilna nevtropenija pojavi kljub uporabi G-CSF, je pri naslednjih ciklih priporočljivo odmerek topotekana zmanjšati za nadaljnjih 20 % na 0,45 mg/m²/dan. Pri bolnicah pri katerih se število trombocitov zmanjša pod 10 x 10^9/l je pri naslednjih ciklih priporočljivo odmerek topotekana zmanjšati za 20 % na 0,60 mg/m²/dan. *Odmerjanje pri bolnikih z ledvično okvaro* Za zdravljenje bolnikov z očistkom kreatinina < 20 ml/min ne moremo priporočti ustreznih odmerkov, saj imamo premalo izkušenj. Omejena količina podatkov, ki je na voljo, kaže, da je treba pri zdravljenju bolnikov z zmerno ledvično okvaro odmerek zmanjšati. **Kontraindikacije** Topotekan je kontraindiciran pri bolnikih, ki imajo v anamnezi hudo preobčutljivostno reakcijo na topotekan ali katero koli pomožno snov; bolnicah, ki so noseče ali dojijo; bolnikih, ki imajo hudo depresijo kostnega mozga že pred začetkom prvega cikla, kar je razvidno iz izhodiščnega števila nevtrofilcev < 1,5 x 10^9/l in/ali števila trombocitov 100 x 10^9/l. **Posebna opozorila in previdnostni ukrepi** Hematološka toksičnost je odvisna od odmerka, zato je treba bolnikom redno nadzorovati celotno krvno sliko, vključno s trombociti. Kot pri uporabi drugih citotoksičnih zdravil so tudi pri uporabi topotekana poročali o pojavu mielosupresije. O pojavu hude mielosupresije in posledične sepse so poročali pri 5 % bolnikov, ki so se zdravili s topotekanom. Huda sepsa se lahko konča smrtno. Uporaba samega topotekana in topotekana v kombinaciji s cisplatinom je pogosto povezana s pojavom klinično pomembne trombocitopenije. To je treba upoštevati, npr. pri bolnikih, pri katerih obstaja večje tveganje za pojav krvavitve tumorja. Kot je bilo pričakovati, se bolniki v slabšem telesnem stanju (PS>1) slabše odzivajo na zdravilo in pri njih tudi pogosteje opažamo zaplete, kot so zvišana telesna temperatura, okužbe in sepsa. Pomembno je, da se bolnikovo telesno stanje ob začetku zdravljenja natančno oceni, zagotovi, da se ne poslabša na 3. Z uporabo topotekana za zdravljenje bolnikov s hudimi motnjami delovanja ledvic (očistek kreatinina < 20 ml/min) ali s hudo okvaro jetrne funkcije, ki je posledica ciroze (serumski bilirubin ≥ 10 mg/dl), nimamo izkušenj. Pri teh skupinah bolnikov zdravljenje s topotekanom ni priporočljivo. Le manjše število bolnikov z jetrno okvaro (vrednost serumskega bilirubina med 1,5 in 10 mg/dl) je prejelo odmerek 1,5 mg/m² po 5 dni na vsake tri tedne. Pri teh opazili manjši očistek topotekana. Vseeno za sedaj nimamo na voljo zadostne količine podatkov, da bi priporočili odmerjanje za to skupino bolnikov. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij** Topotekan ne zavira encimov človeškega citokroma P450. V populacijski študiji niso zasledili, da bi sočasno dajanje granisetrona, ondansetrona, morfina ali kortikosteroidov pomembneje vplivalo na farmakokinetiko celokupnega topotekana (aktivne in neaktivne oblike). Pri sočasni uporabi topotekana z drugimi kemoterapevtiki je zaradi boljšega prenašanja potrebno zmanjšati odmerek vsakega zdravila. Pri sočasni uporabi s platinovimi spojinami pride do izrazite interakcije, ki je odvisna od zaporedja dajanja zdravil, in sicer od tega ali damo pripravek s platino na 1. all 5. dan dajanja topotekana. Če dajemo cisplatin ali karboplatin na 1. dan dajanja topotekana, je potrebno zaradi boljšega prenašanja zmanjšati odmerek teh zdravil v primerjavi z odmerki, ki jih lahko dajemo, kadar damo platinove spojine na 5. dan uporabe topotekana. **Nosečnost in dojenje** Topotekan med nosečnostjo kontraindiciran. Predklinične raziskave so pokazale, da uporaba topotekana povzroča smrt in deformacijo zarodka oziroma ploda. Ženskam je potrebno svetovati, da med zdravljenjem s topotekanom ne smejo zanositi, v primeru zanositve pa naj o tem takoj obvestijo zdravnika. Topotekan je med dojenjem kontraindiciran. **Neželeni učinki** Zelo pogosti: nevtropenija s sočasno povišano telesno temperaturo, nevtropenija, trombocitopenija, anemija, levkopenija, anoreksija, mukozitis, navzea, bruhanje, diareja, zaprtje, abdominalna bolečina, alopecija, zvišana telesna temperatura, astenija, utrujenost. Pogosti: preobčutljivostna reakcija, vključno z izpuščajem, hiperbilirubinemija, pruritus, občutek slabosti. **Vr** ovojnine in vsebina HYCAMTIN 4 mg je na voljo v škatlah z 1 viala. **Način uporabe** Topotekan se sme uporabljati l ustanovah, ki so specializirane za uporabo citotoksičnih kemoterapevtikov. Uporaba zdravila naj vedno poteka pod nad rom zdravnika z izkušnjami na področju kemoterapije.

Datum priprave informacije: Februar 2007

Pred predpisovanjem, prosimo, preberite celoten povzetek temeljnih značilnosti zdravila.

Literatura: 1 Long H J 3rd et al. J Clin Oncol 2005; 23 (21): 4626–4633

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Merck v onkologiji | *biološko zdravljenje za boljšo kakovost življenja*

Erbitux 2 mg/ml raztopina za infundiranje (skrajšana navodila za uporabo)
Cetuksimab je monoklonsko IgG1 protitelo, usmerjeno proti receptorju za epidermalni rastni faktor (EGFR). Terapevtske indikacije: Zdravilo Erbitux je v kombinirani terapiji z irinotekanom indicirano za zdravljenje bolnikov z metastatskim rakom debelega črevesa in danke, in sicer po neuspešni citotoksični terapiji, ki je vključevala tudi irinotekan. Zdravilo Erbitux je v kombinaciji z radioterapijo indicirano za zdravljenje bolnikov z lokalno napredovalim rakom skvamoznih celic glave in vratu. Odmerjanje in način uporabe: Zdravilo Erbitux 2 mg/ml se daje z intravensko infuzijo prek linijskega filtra. Zdravilo Erbitux pri vseh indikacijah infundirajte enkrat na teden. Začetni odmerek je 400 mg cetuksimaba/m² telesne površine, vsi naslednji tedenski odmerki so vsak po 250 mg/m². Pred prvo infuzijo mora bolnik prejeti premedikacijo z antihistaminikom. Ta premedikacija je priporočljiva tudi pred vsemi naslednjimi infuzijami. Kontraindikacije: Zdravilo Erbitux je kontraindicirano pri bolnikih z znano hudo preobčutljivostno reakcijo (3. ali 4. stopnje) na cetuksimab. Pred začetkom kombiniranega zdravljenja morate upoštevati kontraindikacije za irinotekan ali radioterapijo. Posebna opozorila in previdnostni ukrepi: če pri bolniku nastopi blaga ali zmerna reakcija, povezana z infundiranjem, lahko zmanjšate hitrost infundiranja. Priporočljivo je, da ostane hitrost infundiranja na nižji vrednosti tudi pri vseh naslednjih infuzijah. Če se pri bolniku pojavi huda kožna reakcija (≥ 3. stopnje po kriterijih NCI-CTC), morate prekiniti terapijo s cetuksimabom. Z zdravljenjem smete nadaljevati le, če se je reakcija pomirila do 2. stopnje. Posebna previdnost je potrebna pri oslabljenih bolnikih in pri tistih z obstoječo srčno-pljučno boleznijo. Neželeni učinki: Zelo pogosti (≥ 1/10): dispneja, blago do zmerno povečanje ravni jetrnih encimov, kožne reakcije, blage ali zmerne reakcije, povezane z infundiranjem, blag do zmeren mukozitis. Pogosti (≥ 1/100, < 1/10): konjunktivitis, hude reakcije, povezane z infundiranjem. Pogostost ni znana: hipomagneziemija. Pakiranje: 1 viala po 50 ml. Imetnik dovoljenja za promet: Merck KGaA, 64271 Darmstadt, Nemčija. Podrobne informacije o zdravilu so objavljene na spletni strani Evropske agencije za zdravila (EMEA) http://www.emea.eu.int/

Dodatne informacije so vam na voljo pri: Merck, d.o.o., Dunajska cesta 119, 1000 Ljubljana, tel.: 01 560 3810, faks: 01 560 3831, el. pošta: info@merck.si

[1] ploščatocelični rak glave in vratu
[2] v primerjavi z radioterapijo
[3] Bonner et al. Radiotherapy plus Cetuximab for Squamous - Cell Carcinoma of the Head and Neck. N Engl J Med 2006; 354(6): 567-78

www.oncology.merck.de

MERCK

POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Fentanil Lek 25, 50 in 100 mikrogram/h transdermalni obliži **SESTAVA:** 1 transdermalni obliž vsebuje 2,5 mg, 5,0 mg ali 10,0 mg fentanila. **TERAPEVTSKE INDIKACIJE:** Kronične bolečine, pri katerih je potrebno zdravljenje z opioidnimi analgetiki. **ODMERJANJE IN NAČIN UPORABE:** Odmerek zdravila prilagodite posameznim bolnikom in po vsaki uporabi ovrednotite njegov učinek. *Izbira začetnega odmerka.* Višina odmerka naj temelji na predhodni uporabi opioidov. Pri bolnikih, ki nimajo izkušenj z opioidi in ki opioidov predhodno niso jemali, začetni odmerek ne sme presegati 25 µg/h. Predhodnega zdravljenja z analgetiki ne smete prekiniti prej kot v 12 urah po namestitvi prvega transdermalnega obliža. *Določitev stabilnosti odmerka in vzdrževalnega odmerka.* Transdermalne obliže menjajte v 72-urnih presledkih. Odmerek titrirajte, dokler ne dosežete analgetičnega učinka. Če je analgetični učinek ob koncu začetnega obdobja uporabe neustrezen, lahko odmerek povečujete v tridnevnih presledkih do želenega učinka. *Prehod na drugo zdravljenje ali prenehanje zdravljenja.* Če želite preiti na zdravljenje z drugim opioidom, odstranite transdermalni obliž Fentanil Lek in titrirajte odmerek novega analgetika glede na bolnikovo poročanje o bolečini, dokler ne dosežete ustreznega analgetičnega učinka. Pri nekaterih bolnikih se lahko pojavijo odtegnitveni simptomi. *Uporaba pri otrocih.* Zaradi jakosti odmerkov tega zdravila se uporaba pri otrocih ne priporoča. *Uporaba pri starejših* pri starejših bolnikih je treba biti pozoren na znake prevelikega odmerjanja in odmerek po potrebi zmanjšati. *Uporaba pri bolnikih z okvaro ledvic ali jeter:* pri teh bolnikih je treba biti pozoren na znake prevelikega odmerjanja in odmerek po potrebi zmanjšati. *Uporaba pri bolnikih s povišano telesno temperaturo* med epizodami povišane telesne temperature bo morda potrebno prilagajanje odmerka. **KONTRAINDIKACIJE:** Znana preobčutljivost za fentanil, katerokoli pomožno snov ali lepilo transdermalnega obliža. Hudo okvarjeno delovanje osrednjega živčevja. Sočasna uporaba inhibitorjev MAO ali uporaba v 14 dneh po prenehanju zdravljenja z zaviralci MAO. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Zaradi razpolovnega časa fentanila morate bolnika po pojavu resnega neželenega učinka nadzorovati še 24 ur po odstranitvi transdermalnega obliža. Uporabljene in neuporabljene transdermalne obliže hranite nedosegljive otrokom. Obližev ne smete razdeliti, razrezati ali na kakršenkoli način poškodovati. Fentanil lahko povzroči znatno respiratorno depresijo. Fentanil Lek je treba previdno dajati: bolnikom s kronično pljučno boleznijo, povišanim intrakranialnim tlakom, možganskim tumorjem, boleznimi srca, jeter in ledvic, tistim z zvišano telesno temperaturo, pri starejših bolnikih, bolnikih z miastenijo gravis. *Odvisnost od zdravila:* kot posledica ponavljajoče se uporabe se lahko razvijeta toleranca za učinkovino ter psihološka in/ali fizična odvisnost od nje. *Drugi:* lahko se pojavijo neepileptične (mio)klonične reakcije. **MEDSEBOJNO DELOVANJE Z DRUGIM ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ:** Opioidi, sedativi, hipnotiki, splošni anestetiki, fenotiazini, anksiolitiki, sredstva za sproščanje mišic, sedativni antihistaminiki in alkoholne pijače, ritonavir, ketokonazol, itrakonazol in nekateri makrolidni antibiotiki, petidin in zaviralci monoaminske oksidaze (npr. tranilcipromin), pentazocin, buprenorfin. **VPLIV NA SPOSOBNOST VOŽNJE IN UPRAVLJANJA S STROJI:** Zdravilo ima močan učinek na sposobnost za vožnjo in upravljanje strojev. Bolniki naj se o tem, ali smejo voziti in upravljati stroje, posvetujejo z zdravnikom. **NEŽELENI UČINKI:** Najresnejši neželeni učinek fentanila je respiratorna depresija. Zelo pogosti (> 1/10): zaspanost, glavobol, navzeja, bruhanje, zaprtje, potenje, pruritus. Pogosti (> 1/100, < 1/10): sedacija, zmedenost, depresija, tesnoba, živčnost, halucinacije, zmanjšan apetit, kserostomija, dispepsija, kožne reakcije na mestu uporabe. Občasni (> 1/1000, < 1/100): evforija, amnezija, nespečnost, razdražljivost, tremor, parestezija, motnje govora, bradikardija, tahikardija, hipotenzija, hipertenzija, dispneja, hipoventilacija, hemoptiza, pulmonalna kongestija in faringitis, driska, izpuščaj, eritem, zadrževanje urina. *Preobčutljivostne reakcije* anafilaktične reakcije, laringospazem. *Drugi neželeni učinki:* pri dolgotrajni uporabi se lahko razvijeta toleranca in psihična ali fizioloska odvisnost. Pri nekaterih bolnikih, ki z drugega analgetika preidejo na transdermalne obliže Fentanil Lek, se lahko pojavijo reakcije, značilne za prekinitev zdravljenja z opioidi. **NAČIN IZDAJE ZDRAVILA:** Na zdravniški recept. **OPREMA:** Škatlice s 5 transdermalnimi obliži po 25, 50 in 100 mikrogramov/h. **IMETNIK DOVOLJENJA ZA PROMET Z ZDRAVILOM:** Lek farmacevtska družba d.d., Verovškova 57, Ljubljana, Slovenija. **INFORMACIJA PRIPRAVLJENA:** oktober 2006

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član skupine Sandoz | let razvoja

Lek farmacevtska družba d.d. Verovškova 57, 1526 Ljubljana, Slovenija • www.lek.si

Arimidex®

anastrozol

Takojšnje dopolnilno zdravljenje

pri bolnicah po menopavzi z zgodnjim hormonsko odvisnim invazivnim rakom dojke

Kratka informacija o zdravilu

Ime zdravila
Arimidex 1 mg filmsko obložene tablete

Sestava
Ena tableta vsebuje 1 mg anastrozola.

Indikacije
Adjuvantno zdravljenje žensk po menopavzi, ki imajo zgodnji invazivni rak dojke s pozitivnimi estrogenskimi receptorji. Zdravljenje napredovalega raka dojke pri ženskah po menopavzi. Učinkovitost pri bolnicah z negativnimi estrogenskimi receptorji ni bila dokazana razen pri tistih, ki so imele predhodno pozitiven klinični odgovor na tamoksifen.

Odmerjanje in način uporabe
1 tableta po 1 mg peroralno, enkrat na dan.
Pri zgodnjem raku je priporočljivo trajanje zdravljenja 5 let.

Kontraindikacije
Arimidex je kontraindiciran pri:
- ženskah pred menopavzo,
- nosečnicah in doječih materah,
- bolnicah s hujšo ledvično odpovedjo (očistek kreatinina manj kot 20 ml/min (oziroma 0,33 ml/s)),
- bolnicah z zmernim do hudim jetrnim obolenjem,
- bolnicah, ki imajo znano preobčutljivost za anastrozol ali za katerokoli drugo sestavino zdravila.

Posebna opozorila in previdnostni ukrepi
Menopavzo je potrebno biokemično določiti pri vseh bolnicah, kjer obstaja dvom o hormonskem statusu.
Ni podatkov o varni uporabi Arimidexa pri bolnicah z zmerno ali hudo jetrno okvaro ali hujšo ledvično odpovedjo (očistek kreatinina manj kakor 20 ml/min (oziroma 0,33 ml/s)).
Pri ženskah z osteoporozo ali pri ženskah s povečanim tveganjem za razvoj osteoporoze je treba določiti njihovo mineralno gostoto kosti z denzitometrijo, na primer s slikanjem DEXA na začetku zdravljenja, pozneje pa v rednih intervalih. Po potrebi je treba začeti z zdravljenjem ali preprečevanjem osteoporoze in to skrbno nadzorovati.

Povzetek glavnih neželenih učinkov
Zelo pogosti (≥ 10 %): navali vročine, običajno blagi do zmerni
Pogosti (≥ 1 % in < 10 %): astenija, bolečine / okorelost v sklepih, suhost vagine, razredčenje las, izpuščaji, slabost, diareja, glavobol (vsi običajno blagi do zmerni)
Arimidex znižuje nivo estrogena v obtoku, zato lahko povzroči zmanjšanje mineralne kostne gostote, kar pomeni za nekatere bolnike zvečano tveganje za zlome.

Medsebojno delovanje z drugimi zdravili
Zdravila, ki vsebujejo estrogen, ne smete dajati sočasno z Arimidexom, ker bi se njegovo farmakološko delovanje izničilo. Tamoksifena se ne sme uporabljati skupaj z Arimidexom, ker lahko pride do zmanjšanja njegovega delovanja.

Režim izdajanja zdravila
Rp/Spec

Datum priprave informacije
Februar 2007

Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila.

Dodatne informacije in literatura so na voljo pri:
AstraZeneca UK Limited
Podružnica v Sloveniji
Verovškova 55, Ljubljana

in na spletnih straneh:
www.breastcancersource.com
www.arimidex.net

AstraZeneca
ONKOLOGIJA

emodal 20 mg; 100 mg, 250 mg. Sestava zdravila Vsaka kapsula zdravila Temodal vsebuje 20 mg, 100 mg ali 250 mg temozolamida.**Terapevtske indikacije** Temodal apsule so indicirane za zdravljenje bolnikov z: - za zdravljenje novo diagnosticiranega glioblastoma multiforme, sočasno z radioterapijo in kasneje kot monoterapija, - naligním gliomom, na primer multiformnim glioblastomom ali anaplastičnim astrocitomom, ki se po standardnem zdravljenju ponovi ali napreduje. **Odmerjanje in način porabe** Temodal smejo predpisati le zdravniki, ki imajo izkušnje z zdravljenjem možganskih tumorjev. **Odrasli bolniki z novo diagnosticiranim glioblastomom multiforme** Temodal se uporablja v kombinaciji z žariščno radioterapijo (faza sočasne terapije), temu pa sledi do 6 ciklov monoterapije z temozolomidom.**Faza sočasne terapije** Zdravilo Temodal naj bolnik jemlje peroralno v odmerku 75 mg/m² na dan 42 dni, sočasno z žariščno radioterapijo (60 Gy, danih v 30 delnih odmerkih). Odmerka ne boste zmanjševali, vendar se boste vsak teden odločili o morebitni odložitvi jemanja temozolomida ali njegovi ukinitvi na podlagi kriterijev hematološke in nehematološke toksičnosti. Zdravilo Temodal lahko bolnik jemlje ves čas 42-dnevnega obdobja sočasne terapije do 49 dni, če so izpolnjeni vsi od naslednjih pogojev: absolutno število nevtrofilcev $\geq$ 1,5 x 10⁹/l, število trombocitov $\geq$ 100 x 10⁹/l, skupni kriteriji toksičnosti (SKT) za nehematološko toksičnost $\leq$ 1. stopnje (z izjemo alopecije, slabosti in bruhanja). Med zdravljenjem morate pri bolniku enkrat na teden pregledati celotno krvno sliko. **Faza monoterapije** Štiri tedne po zaključku faze sočasnega zdravljenja z zdravilom Temodal in radioterapijo naj bolnik jemlje zdravilo Temodal do 6 ciklov monoterapije. V 1. ciklu (monoterapija) je odmerek zdravila 150 mg/m² enkrat na dan 5 dni, temu pa naj sledi 23 dni brez terapije. Na začetku 2. cikla odmerek povečajte na 200 mg/m², če je SKT za nehematološko toksičnost za 1. cikel stopnje $\leq$ 2 (z izjemo alopecije, slabosti in bruhanja), absolutno število nevtrofilcev (AŠN) $\geq$ 1,5 x 10⁹/l in število trombocitov $\geq$ 100 x 10⁹/l. Če odmerka niste povečali v 2. ciklusu, ga v naslednjih ciklusih ne smete povečevati. Ko pa odmerek enkrat povečate, naj ostane na ravni 200 mg/m² na dan v prvih 5 dneh vsakega naslednjega ciklusa, razen če nastopi toksičnost. Med zdravljenjem morate pregledati celotno krvno sliko na 22. dan (21 dni po prvem odmerku zdravila Temodal). **Ponavljajoči se ali napredujoči maligni gliom: Odrasli bolniki** Posamezen ciklus zdravljenja traja 28 dni. Bolniki, ki še niso bili zdravljeni s kemoterapijo, naj jemljejo Temodal peroralno v odmerku 200 mg/m² enkrat na dan prvih 5 dni, temu pa naj sledi 23-dnevni premor (skupaj 28 dni). Pri bolnikih, ki so že bili zdravljeni s kemoterapijo, je začetni odmerek 150 mg/m² enkrat na dan, v drugem ciklusu pa se poveča na 200 mg/m² enkrat na dan 5 dni, če ni bilo hematoloških toksičnih učinkov. **Pediatrični bolniki** Pri bolnikih, starih 3 leta ali starejših, posamezen ciklus zdravljenja traja 28 dni. Temodal naj jemljejo peroralno v odmerku 200 mg/m² enkrat na dan prvih 5 dni, potem pa naj sledi 23-dnevni premor (skupaj 28 dni). Otroci, ki so že bili zdravljeni s kemoterapijo, naj prejmejo začetni odmerek 150 mg/m² enkrat na dan 5 dni, s povečanjem na 200 mg/m² enkrat na dan 5 dni v naslednjem ciklusu, če ni bilo hematoloških toksičnih učinkov. **Bolniki z motnjami v delovanju jeter ali ledvic** Pri bolnikih z blagimi ali zmernimi motnjami v delovanju jeter je farmakokinetika temozolomida podobna kot pri tistih z normalnim delovanjem jeter. Podatki o uporabi zdravila Temodal pri bolnikih s hudimi motnjami v delovanju jeter (razred III po Child-u) ali motnjami v delovanju ledvic niso na voljo. Na podlagi farmakokinetičnih lastnosti temozolomida obstaja majhna verjetnost, da bo pri bolnikih s hudimi motnjami v delovanju jeter ali ledvic potrebno zmanjšanje odmerka zdravila. Kljub temu je potrebna previdnost pri uporabi zdravila Temodal pri teh bolnikih. **Starejši bolniki** Analiza farmakokinetike je pokazala, da starost ne vpliva na očistek temozolomida. Kljub temu je potrebna posebna previdnost pri uporabi zdravila Temodal pri starejših bolnikih. **Način uporabe** Temodal mora bolnik jemati na tešče. Temodal kapsule mora bolnik pogoltniti cele s kozarcem vode in jih ne sme odpirati ali žvečiti. Predpisani odmerek mora vzeti v obliki najmanjšega možnega števila kapsul. Pred jemanjem zdravila Temodal ali po njem lahko bolnik vzame antiemetik. Če po zaužitju odmerka bruha, ne sme še isti dan vzeti drugega odmerka. **Kontraindikacije** Temodal je kontraindiciran pri bolnikih, ki imajo v anamnezi preobčutljivostne reakcije na sestavine zdravila ali na dakarbazin (DTIC). Temodal je kontraindiciran tudi pri bolnikih s hudo mielosupresijo. Temodal je kontraindiciran pri ženskah, ki so noseče ali dojijo. **Posebna opozorila in previdnostni ukrepi** Pilotno preskušanje podaljšane 42-dnevne sheme zdravljenja je pokazalo, da imajo bolniki, ki so sočasno prejemali zdravilo Temodal in radioterapijo, še posebej veliko tveganje za nastanek pljučnice zaradi okužbe s *Pneumocystis carinii* (PCP). Profilaksa proti tovrstni pljučnici je torej potrebna pri vseh bolnikih, ki sočasno prejemajo zdravilo Temodal in radioterapijo v okviru 42-dnevne sheme zdravljenja (do največ 49 dni), ne glede na število limfocitov. Če nastopi limfopenija, mora bolnik nadaljevati s profilakso, dokler se limfopenija ne povrne na stopnje $\leq$ 1. **Antiemetična terapija:** Z jemanjem zdravila Temodal sta zelo pogosto povezana slabost in bruhanje. **Laboratorijske vrednosti** Pred jemanjem zdravila morata biti izpolnjena naslednja pogoja za laboratorijske izvide: ANC mora biti $\geq$ 1,5 x 10⁹/l in število trombocitov $\geq$ 100 x 10⁹/l. Na 22. dan (21 dni po prvem odmerku) ali v roku 48 ur od navedenega dne, morate pregledati celotno krvno sliko in jo nato spremljati vsak teden, dokler ni ANC nad 1,5 x 10⁹/l in število trombocitov nad 100 x 10⁹/l. Če med katerimkoli ciklusom ANC pade na $<$ 1,0 x 10⁹/l ali število trombocitov na $<$ 50 x 10⁹/l, morate odmerek zdravila v naslednjem ciklusu zmanjšati za eno odmerno stopnjo. Odmerne stopnje so 100 mg/m², 150 mg/m² in 200 mg/m². Najmanjši priporočeni odmerek je 100 mg/m². **Moški bolniki** Temozolomid lahko deluje genotoksično, zato morate moškim, ki se zdravijo z temozolomidom svetovati, da naj ne zaplodijo otroka še šest mesecev po zdravljenju. **Interakcije** Sočasna uporaba zdravila Temodal in ranitidina ni povzročila spremembe obsega absorpcije temozolomida ali monometiltriazenoimidazol karboksamida (MTIC). Jemanje zdravila Temodal s hrano je povzročilo 33 % zmanjšanje Cmax in 9 % zmanjšanje površino pod krivuljo (AUC). Ker ne moremo izključiti možnosti, da bi bila sprememba Cmax lahko klinično pomembna, naj bolniki jemljejo zdravilo Temodal brez hrane. Analiza populacijske farmakokinetike v preskušanjih druge faze je pokazala, da sočasna uporaba deksametazona, proklorperazina, fenitoina, karbamazepina, ondansetrona, antagonistov receptorjev H2 ali fenobarbitala ne spremeni očistka temozolomida. Sočasno jemanje z valprojsko kislino je bilo povezano z majhnim, a statistično značilnim zmanjšanjem očistka temozolomida. Uporaba zdravila Temodal v kombinaciji z drugimi mielosupresivnimi učinkovinami lahko poveča verjetnost mielosupresije. **Nosečnost** Študij na nosečih ženskah ni bilo. Predklinične študije na podganah in kuncih z odmerkom 150 mg/m2 so pokazale teratogenost in/ali toksičnost za plod. Zato naj noseče ženske načeloma ne bi jemale zdravila Temodal. Če pa je uporaba v času nosečnosti nujna, morate bolnico opozoriti na možne nevarnosti zdravila za plod. Ženskam v rodni dobi svetujte, naj med zdravljenjem z zdravilom Temodal preprečijo zanositev. **Dojenje** Ni znano, ali se temozolomid izloča v materino mleko, zato ženske, ki dojijo, ne smejo jemati zdravila Temodal. **Neželeni učinki** V kliničnih preskušanjih so bili najpogostnejši neželeni učinki, povezani z zdravljenjem, prebavne motnje, natančneje slabost (43 %) in bruhanje (36 %). Oba učinka sta bila ponavadi 1. ali 2. stopnje (od 0 do 5 epizod bruhanja v 24 urah) in sta prenehala sama ali pa ju je bilo mogoče hitro obvladati s standardnim antiemetičnim zdravljenjem. Incidenca hude slabosti in bruhanja je bila 4 %. **Laboratorijski izvidi:** Trombocitopenija in nevtropenija 3. in. 4. stopnje sta se pojavili pri 19 % in 17 % bolnikov, zdravljenih zaradi malignega glioma. Zaradi njiju je bila potrebna hospitalizacija in/ali prekinitev zdravljenja z zdravilom Temodal pri 8 % in. 4 % bolnikov. Mielosupresija je bila predvidljiva (ponavadi je pojavila v prvih nekaj ciklusih in je bila najizrazitejša med 21. in 28. dnem), okrevanje pa je bilo hitro, ponavadi v 1 do 2 tednih. Opazili niso nobenih dokazov kumulativne mielosupresije. Trombocitopenija lahko poveča tveganje za pojav krvavitev, nevtropenija ali levkopenija pa tveganje za okužbe.**Imetnik dovoljenja za promet** SP Europe 73, rue de Stalle B-1180, Bruselj, Belgija. **Način in režim izdaje** Zdravilo se izdaja samo na recept, uporablja pa se pod posebnim nadzorom zdravnika specialista ali od njega pooblaščenega zdravnika. **Datum priprave informacije** januar 2006 Podrobnejše informacije o zdravilu Temodal dobite na sedežu podjetja.

Priprava informacije Schering-Ploug, november 2006.

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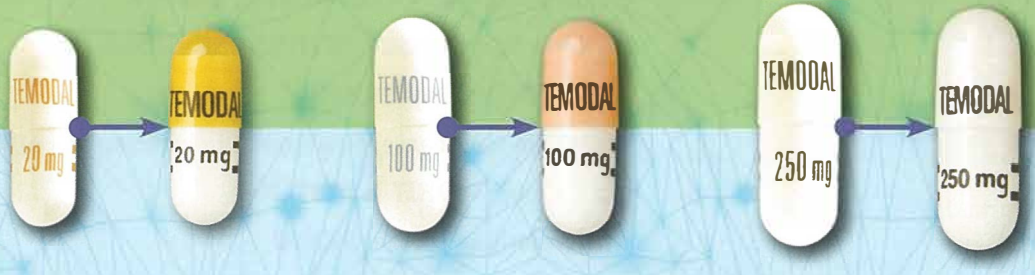

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Dent RAG, Cole P. *In vitro* maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981; **43:** 486-95.

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Evans R, Alexander P. Mechanisms of extracellular killing of nucleated mammalian cells by macrophages. In: Nelson DS, editor. *Immunobiology of macrophage.* New York: Academic Press; 1976. p. 45-74.

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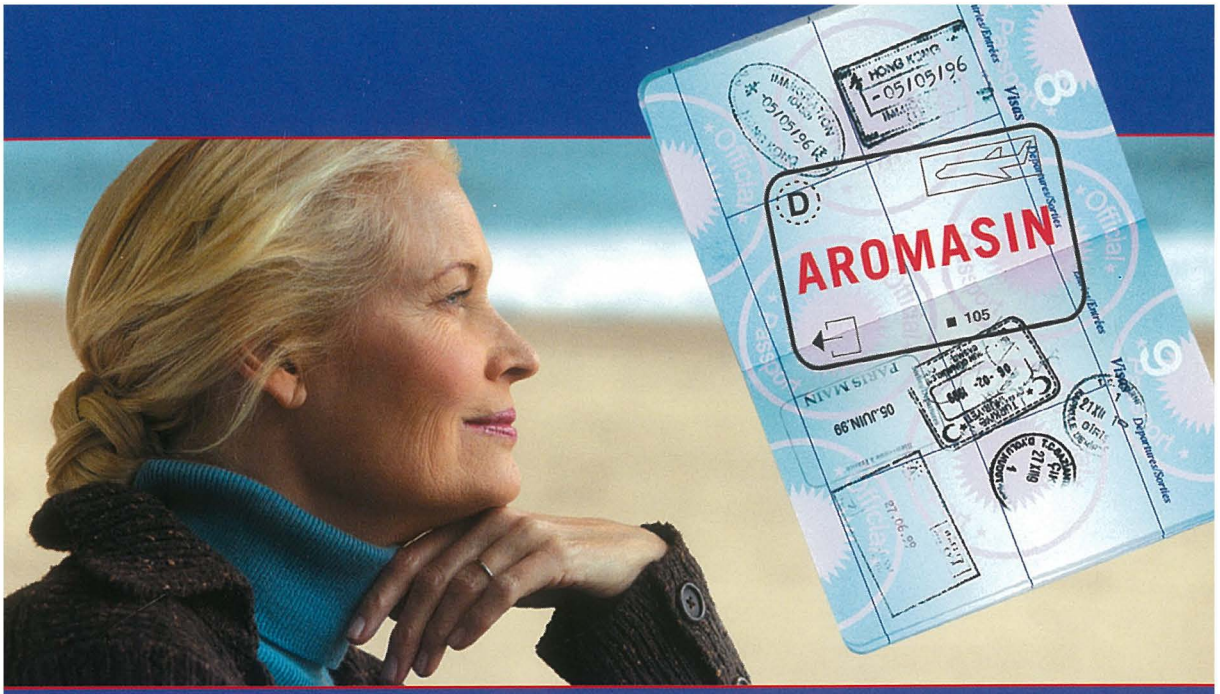

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Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

Podrobnejše informacije o zdravilu so na voljo pri:
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Letališka cesta 3c, 1000 Ljubljana

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