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Dear Colleagues,

It is with great pleasure that I announce that the First Surgical Department of the Metaxas Anticancer Hospital (Athens, Greece), headed by Dr. John Spiliotis, has just received notification from the European Society of Surgical Oncology that it has been formally recognised as one of the training centres in the application of Hyperthermic Intra- Peritoneal Chemotherapy (HIPEC).

Since we all know Greece is experiencing a "brain drain" a period during which a significant number of promising young doctors is being forced to leave Greece and continue their training and education abroad, such recognitions of training centres within the country are exceptionally important and may even, to some degree, reverse the phenomenon.

As surgical oncologists we are very proud of this training centre and all it represents. Perhaps we are justified in the hope that we can make a difference and that even to a small extent, something can change for the better in the country.

Sincerely,

Odysseas Zoras

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EDITORIAL

Surgical infections and the cancer patient

E. de Bree

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THE HISTORY OF SURGICAL INFECTIONS

The management of surgical site infection has a long history and continues to be a major challenge for surgeons in all specialities.[1] Ambroise Paré detremined that the topical treatment of traumatic wounds influenced the outcome. His substitution of a turpentine-based topical treatment, as opposed to the boiled oil and the cauterization method, was the beginning for antisepsis at the injury site. In the 17th century, the Dutch Antoni van Leeuwenhoek first observed bacteria, which had not been considered of pathogenic significance up to that time. In the 18th century, the Scottish surgeon John Hunter observed the value of open wound management and the delay of closure of battlefield wounds. The Hungarian Semmelweis, working in Vienna, identified the role of obstetricians in and the potential of introducing a toxin or poison into birthing women during pre-partum examination. He demonstrated that obstetricians who washed hands with a sodium hypochlorite solution reduced the rate of 'child bed fever'. In the 19th century, it was Louis Pasteur who developed the germ theory of disease, while Robert Koch developed the scientific evidence to prove this theory. Sir Joseph Lister, a British surgeon, was the pioneer in aseptic surgery. He successfully introduced carbolic acid (now known as phenol) to sterilize surgical instruments and to clean wounds, which led to a reduction in post-operative infections and made surgery safer for patients. He instructed surgeons under his responsibility to wear clean gloves and to wash their hands before and after operations with carbolic acid solutions. The discovery of penicillin and the development of sulfa compounds in the late 1920 and in the 1930s resulted in specific chemotherapy (Paul Ehrlich's term) becoming the mainstay for the treatment of infection. Thus, after World War II, antibiotics were widely deployed for the treatment of infection, with different antibiotics being used against different organisms. Microbial resistance patterns developed for specific pathogens and this required the development of new drugs, or the re-engineering of older ones.

The treatment of clinical infections largely became the purview of internal medicine practitioners. It was William Altemeier who pioneered interest in the treatment and prevention of infectious problems that were unique to the surgical patient. In the 1950s, Altemeier and others began to look at antibiotics as a potential avenue not only

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for treating infection, but to prevent infections in the patient undergoing invasive procedures. However, early clinical trials failed to demonstrate any clinical benefit, most probably because of the heterogeneity of the patient populations and the initiation of antibiotic administration in the postoperative period. Ashley Miles at the Lister Institute in London and John Burke from Boston became the fathers of preventive antibiotics in surgery by jointly demonstrating that antibiotics needed to be administered before the surgical intervention to achieve benefit. In 1969, Hiram Polk provided proof of the concept in a randomized clinical trial. Thus, the use of antibiotics and the evolution of preventive strategies became commonplace in surgical care.

SURGICAL INFECTIONS AND THE CANCER PATIENT

Surgical site infections rate have dramatically improved since the times of Ambroise Paré and Joseph Lister. However, the design of surgical interventions has become more innovative with extensive surgical oncology efforts and the general deployment of prosthetic material to replace affected tissues. The surgical host clearly becomes more susceptible with increasing age at the time of intervention, more advanced disease at the time of operation and immunosuppression, either associated with therapeutic interventions (e.g. corticosteroids) or loss of haemostasis (e.g. trauma, shock, resuscitation).

Infectious diseases are leading causes of morbidity and mortality in patients with cancer due to immunodeficiencies that are inherent to underlying malignancies as well as acquired as a result of cancer therapies. Infections continue to evolve as a result of new potent immunomodulatory therapies, the resulting host immunodeficiencies and anti-infective prophylaxis practices. As a result, the spectrum of infections is continually changing. This provides constant diagnostic and therapeutic challenges for clinicians. In this issue, Kritsotakis and Stamatiou discuss the increased susceptibility of surgical cancer patients to infectious complications and the development and implementation of strategies for preventing such infectious complications.[2]

The prevention of surgical site infections in cancer patients does not only comprise of principles of antisepsis and antimicrobial prophylaxis against the major bacterial, viral and fungal disease, but also concerns surgical techniques.[3] Meticulous care during surgical procedures, as well as improvement of the surgical technique and post-operative care of patients aim to reduce the risk of surgical infection and its complications. In this issue, the influence of the routine use of abdominal drains during common oncologic operations on the incidence of surgical site infections is reviewed.[4] It appears that in most cases the routine use of abdominal drainage does not decrease, but, instead, may even increase, the risk of surgical site infections.

It is not only that cancer and its treatment modalities have an impact on the risk of infections in cancer patients, but the infections themselves may also have an effect on cancer incidence and outcome. In this issue, Koronidou and Stamatiou discuss the role of infectious agents in the pathogenesis of various malignancies. As they demonstrate, many experimental and clinical data are available, but many details regarding the relation between infectious agents and development of malignancies are not clear yet. Finally, the fact that surgical site infections may have an adverse effect on survival in cancer patients is discussed by Michelakis and Stamatiou.[5] It appears that surgical site infections are associated with impaired survival in breast, gastric and colorectal cancer, while for melanoma and soft tissue sarcoma such evidence has not yet been published.

Consequently, in this issue of the journal Hellenic Surgical Oncology, various highly interesting aspects of the relation between (surgical) infections and the (surgical) cancer patient are stressed. The knowledge regarding this relationship is continuously evolving, rendering prevention

and management of infectious disease in (future) cancer patients a challenge for clinicians. The related topics have been presented more briefly in a inspiring round table discussion, chaired by Professor Odysseas Zoras at the 14th Greek Congress on Surgical Infections (14ο Πανελληνιο Συνέδριο Χειρουργικών Λοιμώξεων),[7] which was held from May 29 to June 1, 2015 in Chersonisos, Crete and which was presided over by Professor Gerorge Chalkiadakis.

REFERENCES

1. Fry D. Preface. *In:* Surgical infections. Frey (ed). JP Medical Publishers, London, 2013; pages V-VI.
2. Kritsotakis E, Stamatiou D. Immunosuppression and infections in the surgical cancer patient. *Hell Surg Oncol* 2015; 6: 9-15.
3. Pomokova D, Segal BH. Prevention of infection in cancer patients. *In:* Infectious complications in cancer patients. Stosor V, Zembower TR (eds). Springer, Cham, Switzerland, 2014; pages 485-511.
4. de Bree E. Does the routine use of a drain decrease the risk of surgical site infections in oncological abdominal surgery? *Hell Surg Oncol* 2015; 6: 16-23
5. Koronidou K, Stamatiou D. Infection as a cause of carcinogenesis. *Hell Surg Oncol* 2015; 6: 24-36.
6. Michelakis D, Stamatiou D. Surgical infection and cancer recurrence. *Hell Surg Oncol* 2015; 6: 37-42
7. http://www.surgical-infections2015.gr. Accessed June 10, 2015.

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REVIEW

Immunosuppression and infections in the surgical cancer patient

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ABSTRACT

The normal human individual possesses an impressive and effective defence system against microbial enemies. The immune system comprises innate physical barriers as well as acquired immunity. An intact immune system offers protection against most microbial aggressors through a complex interrelationship of protecting surfaces, cells and soluble factors. The cancer patient faces different levels of immunosuppression. Both the underlying malignancy and the therapy can lead to impaired immunity and increase the risk of infectious complications. Extensive surgery increases the risk of infection in cancer patients. Surgery elicits profound changes in the immune, neuroendocrine, and metabolic systems, which constitute the "stress response". The surgical stress and the inflammatory responses affect the immune system and increase the cancer patient's susceptibility to infectious complications. Additionally anaesthesia and variable perioperative factors, such as blood transfusions, pain, and hyperglycaemia can further disrupt the performance of the immune system. Understanding the postsurgical disruptions in immune homeostasis may aid the surgeon and anaesthesiologist in choosing techniques that preserve and/or enhance immune function. In the last decades, the most substantive change in the area of infection control has been a shift in emphasis from control of infections to developing and implementing strategies for preventing healthcare-associated infections. Ensuring adherence to the basic tenets of infection prevention is very important for the cancer patient who is already immune-compromised and at increased risk of infections.

KEY WORDS: immunosuppression, infections, surgical cancer patient

INTRODUCTION

Immunosuppression is a reduction of the activation or efficacy of the immune system. In this state, the immune system's ability to fight infectious disease is compromised or entirely absent. Most cases of immunodeficiency are acquired (secondary deficiency) but some people are born with defects in their immune system (primary deficiency). An immunocompromised person may be particularly vulnerable to opportunistic infections, in addition to normal infections that could affect anyone.

Cancer patients' morbidity and mortality are highly associated with their infectious complications. In patients with underlying haematological

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malignancies autopsy studies reveal that approximately 60% of deaths are infection related.[1,2] In addition 50% of cancer patients with solid organ tumors are estimated to have an infection as either the primary or an associated cause of death.[3,4]

THE IMMUNE SYSTEM

The immune system has always been divided into the innate ("natural") and adaptive ("acquired") immune system due to the difference in primary primitive versus secondary more sophisticated immune responses. However, the innate and adaptive systems have considerable overlap and are highly associated. The innate immune system activates and orchestrates the adaptive immune system.

Innate immunity can be thought of the body's first line of defence and includes physical barriers, such as skin and mucous membranes, as well as pre-formed molecules and cells. Innate immunity is nonspecific, rapid, and does not require prior antigenic exposure for activation. Cells can detect evolutionary conserved microbial sequences that are invariant among a class of pathogens allowing them to initiate an immediate attack without previous contact.

Adaptive immunity is specific, requires prior antigenic exposure, is enhanced by repeat exposure to a pathogen, and has memory. Initiation of the immune response begins when a mononuclear phagocyte ingests an antigen and then presents the antigenic peptide fragment on its membrane (antigen presenting cell [APC]). This stimulates the production and amplification of T and B-lymphocyte clones specific for that antigen. Both branches contain cellular and humoral components.

IMMUNOSUPPRESSION IN THE CANCER PATIENT

The cancer patient faces many factors that predispose to infection. These are traditionally divided into host associated and treatment associated factors. In most cases multiple factors are encountered simultaneously.[5] The first line of defence is provided by the innate immune system. It is composed of anatomical barriers and humoral factors that aid in the inflammatory response.

Anatomical barriers of the skin and mucous membranes are impermeable to most of the infectious agents. Protective processes work in conjunction with these barriers, such as desquamation of skin epithelium, ciliary movement, peristalsis, and production of saliva and tears. Secretions such as fatty acids, lysozyme, phospholipase, and surfactant may further inhibit the colonization of organisms, primarily bacteria. In addition to the barriers, the normal flora of these sites can prevent the colonization of pathogenic organisms by competing for nutrients or attachment to cell surfaces. These barriers can be compromised by malignant invasion and mechanical obstruction and result in being non protective for the cancer patient.[5,6] Skin tumours increase the risk of skin and soft tissue infections and for bacteraemia. Tumours of the oral cavity and nasopharynx result in local infections in the mouth and upper respiratory system. Tumours of the gastrointestinal tract can invade the mucosa and cause local abscess formation, bacteraemia, and perforation. The genitourinary female tract can be invaded by gynaecological tumours which predispose to infections.

Deficits in the humoral components of the innate immune system also predispose to infection.[7,8] Complement deficiencies predispose to infection through ineffective opsonization and lytic activity. Alterations in coagulation can compromise vascular permeability and diminish chemotaxis of phagocytic cells. Lysozyme can disrupt the bacterial cell wall and interleukin-1 induces fever and production of acute phase proteins involved in opsonization. Deficiencies in these components increase the risk of bacterial infections. Deficiencies in interferon predispose to viral infections because it is important in limiting viral replication.

The innate immune system also contains cellular components that facilitate phagocytosis. The cellular innate defences respond rapidly when anatomical and humoral defences are breached. Macrophages, dendritic cells, and mast cells have an important role in phagocytosis and intracellular microbial killing. Macrophages and dendritic cells also function as antigen-presenting cells (APCs) to present ingested foreign antigens on their surfaces to other cells of the immune system. Neutrophils are the most important cells for defence against bacterial infections in cancer patients. Patients with haematological malignancies (leukaemia or lymphoma) or solid tumours with metastatic disease that infiltrates the bone marrow can result in neutropenia.[9] These patients are more susceptible to infections.

Adaptive immunity is comprised of both humoral and cellular components, mediated through B and T lymphocytes, respectively. Under proper antigenic stimulation, B lymphocytes differentiate into immunoglobulin-producing cells. By producing opsonizing antibodies they promote the phagocytosis of bacteria, particularly encapsulated bacteria. Patients with defects in humoral immunity are more susceptible to infections with organisms such as S. pneumoniae, H. influenza, and N. meningitidis. During cell-mediated immunity, various T lymphocyte subsets are activated and develop into effector T cells, including cytotoxic T lymphocytes and T helper cells of TH1 and TH2 subsets. The deficiencies of cell-mediated immunity are associated with intracellular pathogens, including bacteria (Salmonella, legionella), mycobacteria (M. tuberculosis), viruses (VZV, EBV), and protozoa (Toxoplasma).

The risk of infection is also increased in cases of impairment of various organ consequent to tumour invasion or mechanical obstruction. Patients with splenectomy or functionally asplenic are at increased risk of infection with encapsulated bacteria and for sepsis.[10] Patients with dysfunction of the central nervous system are commonly vulnerable to infections. They frequently suffer from loss of gag reflex, impaired micturition, impaired mobility and skin breakdown.[11]

COMORBIDITIES

Patients with type 2 diabetes and hyperglycaemia are more likely to be associated with infections and with shorter median survival times.[12] Obesity also increases infection risk, especially those undergoing oncologic surgery.[13] Cancer patients previously infected, including past infections with Mycobacterium tuberculosis and viruses such as HSV, EBV, and CMV, are at increased risk of infection reactivation. Significant weight loss and malnutrition are common among cancer patients. Their poor nutritional status is caused by

Table 1. The components of the human immune system

Immunity	Cellular components	Humoral components
Innate	• Phagocytic cells • Natural killers (NK) • Mast cells • Antigen presenting cells (APC)	• Complement • Acute phase reactants (CRP) • Cytokines
Adaptive	• T Lymphocytes - Koiller - Helper - Memory - Suppressor • B Lymphocytes	• Immunoglobulines

inadequate intake of carbohydrate, protein, and fat and reduced absorption of macronutrients. The nutritional deficiency is associated with increased risk of infection and increased mortality.[14] It is suggested that psychological stress plays an important role in susceptibility to certain infections. Stress, anxiety, and depression, which are frequently present in the cancer patient, are risk factors for acute viral respiratory infections.[15] The immune system is influenced by the stress-mediated activation of the sympathetic nervous system and much remains to be learned regarding the complex interplay between physical health and psychological health in cancer patients.

SURGERY

Surgery is essential to cancer patient care, and at the same time, the most common treatment-associated factor that predisposes to infectious complications. The "surgical stress" response reflects a combination of endocrinological, immunological, and haematological changes occurring after injury/trauma. The immunoinflammatory changes are related to the extension of surgical trauma. The stress response begins with the activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. This activation results in secretion of ACTH, cortisol, catecholamines, aldosterone, and glucagon. This secretion represents an effort to provide the host with energy, retain fluid and salt, and maintain cardiovascular homeostasis. Excessive stress response can result in harmful outcomes to the host such as hyperglycaemia, cardiovascular instability, and immunosuppression. The hypersecretion of cortisol and catecholamines has both anti-inflammatory and immunosuppressant effects.[16] Excessive secretion of cortisol is responsible for reduced aggregation of macrophages and neutrophils at the site of injury, and decreases phagocytosis. In addition, it induces apoptosis in T lymphocytes and promotes Th2 cell dominance.

Cytokines are proteins produced by a variety of cells and are involved with the immune system in modulating the response to surgical stress and infection.[17] There is a delicate balance between the release of pro and anti-inflammatory cytokines. In the case of an unbalanced inflammatory state and an exaggerated anti-inflammatory response,we may observe significant post-operative morbidity from immunosuppression. The direct consequences are nosocomial infections and tumour progression.[18] In the immediate response to surgery and tissue trauma there is an acute hyperinflammatory phase where phagocytic and endothelial cells produce IL-1 and TNF-α. The inflammatory cascade is activated by these cytokines in an attempt to control tissue damage and maintain homeostasis. In the later response to tissue trauma, we observe a second cytokine release of IL-6 that has both pro- and anti-inflammatory effects. The immediate (early) proinflammatory response to surgery is a result of predominance of the Th1 cytokines (IL-2, IL-12). The increased and prolonged surgical stress, due to the release of glucocorticoids and catecholamines, results in a shift towards the anti-inflammatory Th2 predominance (IL-4, IL-6). This shift is responsible for the consequential depressed cellular immunity and increases the susceptibility to infections of the operated cancer patient.[19,20]

ANALGESICS AND ANAESTHESIA

Intravenous opioids are often used and are very important in the treatment of cancer pain. Morphine and other related opioids may have significant adverse consequences due to their immunological influences. They are correlated to suppression of innate and acquired immune responses, as demonstrated in human cells and in animal cells.[21,22] This results in decreased resistance to infection and sometimes to cancer progression.[23,24] The major immunological effect is the suppression of the natural killer (NK) cells, which are crucial for the rejection of tumour cells and eradication of viruses.

The effects of anaesthesia have also been studied in vitro in certain animal studies. Intravenous anaesthetic agents such as propofol and thiopental are correlated to NK cell activity suppression.[25] Volatile anaesthetics have been demonstrated to have properties of immunomodulation and to suppress the activity of NK cells.[26] Particularly sevoflurane causes an altered release of cytokines such as IL-1 and TNF responsible for immunosuppression.[27]

Local anaesthetics (lidocaine, ropivacaine) and regional anaesthesia (epidural) in various retrospective studies are not correlated to immunosuppressive effects. It seems that the use of local and regional anaesthesia can influence the long-term outcome of cancer surgery.[28] First of all, there is an attenuation of the intrinsic immunosuppression from surgery. The patient does not need as much opioid treatment and requires a lower dose of inhalational anaesthetics. In this way, their immunosuppressive effects are avoided. More studies are needed to elucidate the benefits of local and regional anaesthetics.

TREATMENT-ASSOCIATED FACTORS

In addition to surgery, irradiation and chemotherapy are essential for cancer patient care. Both treatments are not without risk and increase the risk of infection. Preoperative irradiation is associated with increased infectious complications in breast, respiratory, and gastrointestinal cancers.[29,30] Irradiation is correlated to local tissue damage and obstruction due to stenosing lesions, both of which increase the risk of infection. Another adverse effect of irradiation is bone marrow depression and neutropenia which result in depression of cellular immune function. A very common reaction to radiation is local tissue inflammation and predisposes to infection. We may observe extended dermatitis in previous irradiated areas including erythema, ulceration, and necrosis in extreme cases.

Chemotherapeutic agents predispose cancer patients to infection. The increased risk of infection is mostly correlated to the interruption of anatomical barriers. The ulceration of the gastrointestinal tract results in erosion, invasion by microorganisms and bacteraemia. Bone marrow suppression is substantial in chemotherapy. In addition to the neutropenia, we also observe decreased migration and chemotaxis of neutrophils.[9]

The use of antibiotics and various diagnostic and invasive procedures are correlated to risk infection. An extended and prolonged use of antibiotics in the cancer patient may influence the normal flora and decrease the protection of skin and mucous membranes. More pathogenic and invasive microorganisms can colonize the anatomical barriers and result in severe infections. In addition to altering the endogenous flora, the extended use of antibiotics increases the resistance of microorganisms to antibiotics resulting in patients being more vulnerable to infections. In the hospitalized cancer patient, frequent common invasive procedures can predispose to risk infections. These procedures include central venous catheters, urinary catheters, endoscopy, tracheostomy, and blood transfusions.

PREVENTION

It has already been mentioned above that surgery is essential for cancer patients. The consequent postoperative immunosuppression is correlated to the extent of surgical trauma and postoperative pain. Minimal invasive surgery more often results in less surgical trauma being induced than in conventional surgery. Laparoscopic surgery is correlated to reduced inflammatory response and minimal immunosuppression. Postoperative levels of the proinflammatory cytokines are lower after laparoscopic surgery indicating lower acute inflammatory reaction and clear immunologic advantage. Minimal invasive surgery has many benefits in the treatment of abdominal malignancies and lung cancer. Laparoscopy and thoracoscopy, in addition to the less induced immunosuppression

and less septic complications, are associated with diminished perioperative tumour dissemination, higher survival rates and less frequent metastases. Epidural analgesia is very important in the management of postoperative pain and results in diminished activation of the hypothalamic-pituitary-adrenal axis and less immunosuppression being induced. The perioperative benefits of regional anaesthesia are mentioned above and are correlated to the diminished doses of inhalational and intravenous anaesthetics. For the vulnerable cancer patient the correct use of the antibiotics and the strict adherence to the application of the basic tenets of personal hygiene,are indispensable.

CONCLUSIONS

The patients with neoplastic diseases often suffer from immune deficiencies and are more susceptible to infections. Cancer patients' morbidity and mortality are highly associated with immunosuppression and it is very important to comprehend all host-associated and treatment-associated risk factors in order to avoid infectious complications. Surgery is essential for the cancer patient's treatment but greatly associated with postoperative immunosuppression being induced. The perioperative management of the patient should consider the postoperative surgical stress response and the immunoinflammatory changes. The main effort is to use minimally invasive techniques, when clinically warranted. Laparoscopic surgery attenuates the usual postoperative cytokine cascade and the shift towards a Th2 anti-inflammatory cytokine profile that is associated with immunosuppression. The use of certain anaesthetics/analgesics is crucial in order to avoid intraoperative stress response and improve prognosis. Regional analgesia is very effective in inhibiting the stress response to surgery and limits the doses of intravenous and inhalational anaesthetics that are correlated to immunosuppression. In cancer patient's management, it is very important to prevent immune deficiencies and also to refine therapeutic regimens that are effective. Both are necessary in achieving remission of neoplastic disease and improving quality of life.

REFERENCES

1. Chang HY, Rodriguez V, Narboni G, Bodey GP, Luna MA, Freireich EJ. Causes of death in adults with acute leukemia. *Medicine* (Baltimore)1976; 55: 259-268.
2. Nosari A, Barberis M, Landonio G, et al. Infections in haematologic neoplasms: autopsy findings. *Haematologica* 1991; 76: 135-140.
3. Homsi J, Walsh D, Panta R, Lagman R, Nelson KA, Longworth DL. Infectious complications of advanced cancer. *Support Care Center* 2000; 8: 487-492.
4. Inagaki J, Rodriguez V, Bodey GP. Proceedings: causes of death in cancer patients. *Cancer* 1974; 33: 568-573.
5. Donelly JP, Blijlevens NMA, De Pauw BE. Infections in the immunocompromised host: general principles. In: Mandell GL, Bennett JE, Dolin R Mandell, Doublas, and Bennett's principle and practice of infectious diseases. Churchill Livingstone, Philadelphia, 2009; pages 3781-3792.
6. Viscoli C, Castagnola E. Factors predisposing cancer patients to infection. In: Klastersky K (ed) Infectious complications of cancer. Kluwer Academic, Boston, 1995; pages 1-30.
7. Dorman SE, Uzel G, Roesler J, et al. Viral infections in interferon-gamma receptor deficiency. *J Pediatr* 1999; 135: 640-643.
8. Wagner RR. Cellular resistance to viral infection, with particular reference to endogenous interferon. *Bacteriol Rev* 1963; 27: 72-86.
9. Glauser MP, Zinner SH. Mechanisms of acquisition and development of bacterial infections in cancer patient. In: Klastersky J (ed) Infections in cancer patients. Raven press, New York, 1982; pages 13-30.
10. Van Der Meer JWM. Defects in host-defence mechanisms. In: Rubin RH, Young LS (eds) Clinical approach to infection in the compromised host. Plenum Medical. New York, 1988; pages 41-63.
11. Schimpff SC. Infection in the cancer patient-diagnosis, prevention, and treatment. In: Mandell GL, Bennett JE, Dolin R (eds) Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Churchill Livingstone, New York, 1995; pages 2666-2675.
12. Barone BB, Yeh HC, Snyder CF, et al. Long-term all

cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 2008; 300: 2754-2764.
13. Balentine CJ, Marshall C, Robinson C, et al. Obese patients benefit from minimally invasive colorectal cancer surgery. *J Surg Res* 2010; 163: 29-34.
14. National Cancer Institute. Nutrition in cancer care - for health professional (PDQ®). http://www.cancer.gov/about-cancer/treatment/side-effects/appetite-loss/nutrition-hp-pdq, Accessed July 18, 2015.
15. Falagas ME, Karamanidou C, Kastoris AC, Karlis G, Rafailidis PI. Psychosocial factors and susceptibility to or outcome of acute respiratory tract infections. *Int J Tuberc Lung Dis* 2010; 14: 141-148.
16. Ogama K, Hirai M, Katsube T, et al. Suppression of cellular immunity by surgical stress. *Surgery* 2000; 127: 329-336.
17. Sheeran P, Hall G. Cytokinesin anesthesia. *Br J Anaesth* 1997; 78: 201-219.
18. Angele M, Faist E. Clinical review: Immunodepression in the surgical patient and increased susceptibility to infection. *Critical Care* 2002; 6; 298-305.
19. Salo M. Effects of anaesthesia and surgery on the immune response. *Acta Anaesthesiol Scand* 1992; 36: 201-220.
20. Lin E, Calvano S, Lowry S. Inflammatory cytokines and cell response in surgery. *Surgery* 2000; 127: 117-126.
21. Sacerdote P, Manfredi B, Mantegazza P, Paneral AE. Antinociceptive and immunosuppressive effects of opiate drugs: a structure-related activity study. *Br J Pharmacol* 1997; 121: 834-840.
22. Markovic SN, Knight PR, Murasko DM. Inhibition of interferon stimulation of natural killer cell activity in mice anesthetized with halothane or isoflurane. *Anesthesiology* 1993; 78: 700-706.
23. Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. *Am J Ther* 2004; 11: 354-365.
24. McCarthy L, Wetzel M, Silker JK, Eisenstein TK, Rogers TJ. Opioids, opioid receptors, and the immune response. *Drug Alcohol Depend* 2001; 62: 111-123.
25. Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and profhylactic measures. *Anesth Analg* 2003; 97: 1331-1339.
26. Hole A, Unsgaard G. The effect of epidural and general anaesthesia on lymphocyte functions during and after major orthopaedic surgery. *Acta Anaesthesiol Scand* 1983; 27: 135-141.
27. Mitsuhata H, Shimizu R, Yokohama MM. Suppressive effects of volatile anesthetics on cytokine release in human peripheral blood mononuclear cells. *Int J Immunopharmacol* 1995; 17: 529-534.
28. Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. *Br J Anaesth* 2010; 105: 106-115.
29. Say CC, Donegan W. A biostatical evaluation of complications from mastectomy. Surg Gynecol Obstet 1974; 138; 370-376.
30. Smith MG, Golding PL, Eddleston AL, Mitchell CG, Kemp A, Williams R. Cell-mediated immune responses in chronic liver diseases. *Br J Med* 1972; 1(5799): 527-530.

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REVIEW

Does the routine use of a drain decrease the risk of surgical site infections in oncological abdominal surgery?

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ABSTRACT

The routine use of drains in abdominal surgery remains a subject of debate. The purpose of drainage is the prevention of accumulation of blood, serous fluid, lymph and other peritoneal fluids and, subsequently, of contamination of such fluid collections, in order to decrease the risk of intra-abdominal abscesses. Moreover, drains may help in the early recognition of intra-abdominal bleeding, leakage of gastrointestinal anastomosis or closure, gastrointestinal perforation and pancreatic fluid or bile leakage, as well as in decreasing the need for additional surgical or percutaneous interventions. While in the past abdominal drainage was routinely applied after abdominal oncological surgery, many have called into question the benefit of such drainage. Abdominal drainage may be associated with increased risk of wound infections, intra-abdominal abscesses and impaired anastomotic healing, drain related complications and increased costs. In this review, the existing evidence of the benefit of routine abdominal drainage in common types of oncological surgery is discussed, with emphasis on its effect on surgical site infections (i.e. wound infections and intra-abdominal abscesses).

KEY WORDS: abdominal drain, gastrectomy, pancreatectomy, colorectal surgery, hepatectomy

INTRODUCTION

The use of drains dates back to Hippocrates (460-370 BC), who used linen to keep wounds open after drainage of thorax empyema. Ambroise Pare (1510-1590) was the first to describe drainage of the abdominal cavity, but abdominal drainage had probably been used in practice earlier. Thus, abdominal drainage has a long historic tradition. However, the routine use of drains in abdominal surgery remains a subject of debate. The purpose of drainage is the prevention of accumulation of blood, serous fluid, lymph and other peritoneal fluids and, subsequently, of contamination of such fluid collections, in order to decrease the risk of intra-abdominal infectious fluid collections and abscesses. Moreover, drains may help in the early recognition of intra-abdominal bleeding, leakage of gastrointestinal anastomosis or closure, gastrointestinal perforation and pancreatic fluid or bile

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leakage. In the case of leakage of bowel contents, pancreatic fluid or bile, the drain facilitates the creation of a directed fistula, decreasing the need for additional surgical or percutaneous interventions. While in the past abdominal drainage was routinely applied after abdominal oncological surgery, many have called into question the benefit of such drainage. It is even argued that drains may give rise to infections by allowing entrance of bacteria into the surgical field, resulting in increased risk of wound infections, intra-abdominal abscesses and impaired anastomotic healing. Moreover, drain erosion into surrounding tissue and excessive suction may cause gastrointestinal anastomotic leakage, bowel perforation and bleeding. Further, drains may cause local drain site discomfort, infection, bleeding and hernia, while local pain at the drain site may cause inadequate respiration leading occasionally to pleural effusions, atelectasis and pneumonia. Drain removal may cause pain as well as organ and vessel lesions. Finally, placement of drains may increase operation time, hospital stay and costs.[1-5]

In this review, the existing evidence of the benefit of routine abdominal drainage in common types of oncological surgery is discussed, with emphasis on its effect on surgical site infections. These surgical site infections include wound infections as well as organ related infections, as for example, intra-abdominal abscesses.

DRAIN TYPES AND SURGICAL SITE INFECTION

To determine the role of the routine use of drains in abdominal surgery, it has to be noted that different types of drains exist, each with its advantages and disadvantages. Open, passive drains (for example Penrose drains, named after the American gynaecologist Charles Bingham Penrose (1862–1925)) are usually soft and therefore do not give rise to erosion of surrounding tissue, and are inexpensive, but are associated with an increased risk of bacterial contamination and, consequently, surgical site infections. Closed, suction drains (for example Redon and Jackson-Pratt drains) are associated with higher costs, with lower risk of bacterial contamination and, due to their usually harder texture, with higher risk of erosion of surrounding tissues, while these drains may get occluded more easily when clots are formed in the drain or when surrounding tissue is sucked into the drain. To overcome the latter, sump drains have been used, which can draw out fluids from a cavity by suction through its main channel, while allowing air to enter the cavity through adjacent channels. Sump drains, however, are more expensive, demand more nursing care and have a risk of intra-abdominal surgical site infection by airborne contamination, even when protective filters are positioned at the entrance of the inflow channels.[6,7]

To determine whether the absence or presence of drains per se and whether the type of drains influence intra-abdominal surgical site infection rate, it is best to analyze the proffered data in a clean operation, as for example, a splenectomy.

The role of open abdominal drains as a source of infection has been clearly demonstrated in an old study of Cerise et al.[7] In a rabbit model, they showed that placing an open drain after a splenectomy was associated with an eight times increased risk of bacterial contamination of the splenic bed, when compared with leaving no drain behind. Additionally, in a retrospective analysis of 533 patients who had undergone splenectomy for various reasons, a 25-fold increase of left subphrenic abscess was observed after placement of an abdominal, mainly. Penrose, drain (10% vs. 0.5%, $p < 0.005$). In non contaminated and in potentially contaminated operations, this difference in occurrence of subphrenic abscess was highly significant ($p=0.001$), while in contaminated surgery, for example, with concomitant traumatic large bowel rupture, the observed difference was not statistically significant (8.9% vs. 4%). In contaminated surgery, a subphrenic abscess is most probably caused by contamination of the splenic

bed by intra-abdominal bacteria rather than by exogenous bacteria through the drain.

In a more recent retrospective study,[8] a similar incidence of splenic abscess was observed after placement of a closed suction drain as when no drain was left behind after splenectomy for isolated splenic trauma. The authors concluded that the risk of bacterial contamination through a closed suction drain is considerably low.

Airborne bacterial contamination in sump drains had already been demonstrated in 1974 in the classic research manuscript of Baker and Borchardt.[6] In an *in vitro* model, with a high volume of air aspirated by the suctions source, they found a 100% airborne bacterial contamination rate when no filters were used; when protective filters were used at the inflow channels, this contamination rate was still 47.5%. Low volume air aspiration did not result in bacterial contamination.

In an older study,[9] 78 patients with splenectomy for various reasons were randomized to receive no drain, a Jackson-Pratt closed suction drain or a Penrose drain. All drains, except three, had already been removed within the first 48 postoperative hours, while the other three were removed during the following 48 hours. Drain complications were only seen in the Penrose drain group, which included one subphrenic abscess (4%) and one evisceration of the small bowel through the drain site (4%). It has to be noted that the single formation of an intra-abdominal abscess was observed in a patient with concomitant large bowel injury and hence, most probably, contamination with bowel flora. The authors concluded that the presence or absence of drains per se does not seem significant, but that concomitant bowel injury and the duration of drainage may be significant factors influencing infection.

It is interesting to note that the recommendations for the prevention of surgical site infections from the Center for Disease Control and Prevention include only one small paragraph regarding abdominal drains: "Drains placed through an operative incision increase incisional surgical site infection risk. Many authorities suggest placing drains through a separate incision distant from the operative incision. It appears that surgical site infection risk also decreases when closed suction drains are used rather than open drains. Closed suction drains can effectively evacuate postoperative hematomas or seromas, but timing of drain removal is important. Bacterial colonization of initially sterile drain tracts increases with the duration of time the drain is left in place."[10]

GASTRECTOMY FOR GASTRIC CANCER

Thought of as an important measure to reduce postoperative complications and mortality, abdominal drainage was widely used after gastrectomy for gastric cancer in previous decades. The benefits of abdominal drainage have been questioned by researchers in recent years. Hence, there is no consensus on the routine placement of abdominal drainage after gastrectomy for gastric cancer.

A recent meta-analysis of four randomized trials on the routine use of abdominal drains after gastrectomy for gastric cancer included 438 patients.[2] No statistically significant difference was observed for surgical site infections (wound infections and intra-abdominal abscesses) when the routine use of abdominal drains was compared with the omission of such a drain. Mortality, reoperation rate, incidence of postoperative pneumonia, anastomotic leakage rate and time frame to food intake were also on a par. However, the addition of a drain prolonged the operation time (mean 9.07 min) and post-operative hospital stay (mean 0.69 days) slightly, but statistically significant. Moreover, the use of an abdominal drain led to drain-related complications. Unfortunately, the impact of the type of drain used was not analyzed.

In a recent retrospective study,[11] the association of abdominal drain placement with postoperative outcomes was analyzed in 344 patients who underwent total gastrectomy for gastric ad-

enocarcinoma at seven institutions from the US Gastric Cancer Collaborative. No difference was observed in the rate of any complication (54 vs. 48%, p=0.45), major complication (25 vs. 24%, p=0.90), or 30-day mortality (7 vs. 4%, p=0.51) between the patients with (n=253) and those without an abdominal drain (n=91). In addition, no difference in anastomotic leakage (9 vs. 10%, p=0.90), the need for secondary drainage (10 vs. 9%, p=0.92), or reoperation (13 vs. 8%, p=0.28) was identified. The surgical site infection rate also did not differ significantly (13% vs. 9%, p=0.37). At multivariate analysis, abdominal drain placement was not a significant risk factor of surgical site infection (p=0.40) or any other postoperative complication. Subset analysis, stratified by patients who did not undergo concomitant pancreatectomy (n= 319) or those who experienced anastomotic leakage (n=31), similarly demonstrated no association of abdominal drain placement with reduced complications or mortality.

Also, in a recent retrospective study on the routine use of a low-suction closed silicon abdominal drain after laparoscopic partial gastrectomy for gastric cancer,[12] no benefit of the presence of an abdominal drain could be demonstrated. On the contrary, the use of an abdominal drain was associated with a higher incidence of wound infection (8.9% vs. 3.0%) and intra-abdominal abscess formation (6.7% vs. 3.0%) when compared to the absence of such a drain. However, the number of patients (45 vs. 33) was apparently too small to demonstrate statistically significant differences. Anastomotic leakages were not observed in either group, while leakage of the duodenal stump was statistically non-significantly higher in the group of patients where drainage had been omitted (6.1% vs. 0%).

In conclusion, abdominal drain placement after gastrectomy for gastric cancer is generally associated with neither a decrease in the frequency and severity of adverse postoperative outcomes, including anastomotic leak and mortality, nor a decrease in the need for secondary drainage procedures or reoperation. Therefore, routine use of abdominal drains is not warranted. Contrarily, the insertion of an abdominal drain may increase the incidence of surgical site infections.

PANCREATECTOMY

Pancreatic surgery is burdened with high mortality (about 5%) and morbidity rates (about 50%).[13,14] Pancreatic fistula is the most dreadful complication occurring from 4% to 30% of patients after pancreaticoduodenectomy, according to the definition used; infectious complications occur in about 34% of pancreaticoduodenectomy and intra-abdominal abscess in 14%.[13-15] The use of operative site drains has been considered by most surgeons routine in pancreatic surgery. Usually, multiple catheters are placed in the right and left subhepatic space in relation to biliary and pancreatic anastomoses in order to remove any collections of blood and biliary, lymphatic or pancreatic secretions. The rationale for intra-abdominal drainage is to allow a rapid evacuation of postoperative fluid collections, thus avoiding their infective contamination, and for timely detection of haemorrhage and anastomotic dehiscence.

A recent meta-analysis[1] of the routine use or not of an abdominal drain comprised of two randomized controlled trials and six retrospective studies, including 2773 patients overall. The studies were, in general, heterogeneous regarding kind of disease (benign or malignant) and/or type of surgery (pancreatoduodenectomy, distal pancreatectomy or other). When a drain was used, in most studies it was a closed suction drain, whereas in the remaining studies the type of drain was not specified. The overall complication rate was 30% lower (p=0.04) when routine abdominal drainage was omitted. This difference was mainly caused by the 30% increased fistula formation in the group of patients where drainage was performed (p=0.12). Overall, the risk of an intra-abdominal abscess, as well as the mortality rate, the re-operation rate, radiological intervention rate and length of hos-

pital stay were not statistically different between the two groups of patients.

Another meta-analysis[16] agreed that the routine use of abdominal drains in pancreatic surgery does not generally improve the post-operative outcome. Overall seven studies were included in this meta-analysis, two randomized controlled trials and five non-randomized studies, resulting in a total of 2704 patients. Intra-abdominal drainage showed an increase in the incidence of pancreatic fistula by 2.31 times ($p<0.0001$), the overall occurrence of post-operative complications by 1.52 times ($p<0.00001$) and the re-admission rate by 1.30 times ($p=0.01$). A non-significant correlation was found with the presence of the drainage regarding biliary and enteric fistula, post-operative haemorrhage, intra-abdominal infected collection, wound infection and overall mortality ($p=0.09$) rates.

A most recent meta-analysis[17] which included only the two available randomized controlled trials, involving 316 participants, could not demonstrate significant differences in mortality, overall morbidity, intra-abdominal infection rate, wound infection rate and the need for re-operation, with regard to the use or not of an abdominal drain after pancreatic surgery.

However, when only patients who underwent pancreatoduodenectomy were evaluated in the first met-analysis,[1] the risk of an intra-abdominal abscess was 2.27 times higher ($p=0.04$) and the mortality 2.47 times higher ($p=0.04$) in the group of patients who not had routinely received drainage.

In a recent multi-centre study,[18] 137 patients undergoing pancreatoduodenectomy were randomized to receive or forego an intra-abdominal closed suction drain. The surgical procedure was performed for malignant disease in 95 of the cases. Pancreatoduodenectomy without a drain was associated with higher incidence of intra-abdominal abscess (10% vs. 25%, $p=0.027$). The study was halted early on by the Data Safety Monitoring Board because of an increase in mortality from 3% to 12% ($p=0.097$) in the patients undergoing pancreatoduodenectomy without intra-abdominal drainage. Further, elimination of intra-abdominal drainage was associated with an increase in the number of complications per patient, complication severity, incidence of gastric paresis, intra-abdominal fluid collection and hospital stay. There was no difference in wound infection and fistula formation.

In a single-centre study,[19] a total of 114 eligible patients who underwent standard pancreatic resections and at who were at low risk of postoperative pancreatic fistula according to our institutional protocol (amylase value in drains ≤5000 U/L on the first postoperative day) were randomized on the third postoperative day to receive either early (third postoperative day) or standard drain removal (fifth postoperative day or beyond). There was no evidence of differences between the two groups in mortality at 30 days (0% for both groups) or additional open procedures for postoperative complications (0% versus 1.8%). Early drain removal was associated with a decreased rate of pancreatic fistula ($p=0.0001$), abdominal complications (including intra-abdominal abscess, $p=0.002$), and pulmonary complications ($p=0.007$), whereas the median in-hospital stay was shorter ($p=0.018$) and hospital costs lower (17.0% decrease of 'average' hospital costs, $p=0.02$). Based on the above data, a protocol of selective drainage and optimal timing for removal of drains in pancreatic surgery has been advocated.[20]

In conclusion, routine abdominal drainage is indicated after pancreatoduodenectomy since it decreases the mortality rate and the risk of an intra-abdominal abscess. The routine use of an abdominal drain may be omitted after distal pancreatectomy because it appears to increase the pancreatic fistula rate and the overall complication rate, while it does not beneficially influence the mortality rate and the risk of an intra-abdominal abscess or other complications. In the case of drain insertion, data suggest that early removal may be superior to later removal for patients with low risk of postoperative pancreatic fistula.

HEPATECTOMY

The main reasons for inserting a drain after elective liver resections are prevention of subphrenic or subhepatic fluid collection, the identification and monitoring of post-operative bleeding, the identification and drainage of any bile leak, and the prevention of accumulation of ascitic fluid in cirrhotic patients. However, there are reports that drain use increases the complication rates.

In a meta-analysis[3] of five randomized studies with 465 patients who underwent uncomplicated elective hepatectomy and were allocated to the routine use or not of an abdominal drain, no differences could be demonstrated regarding the incidence of wound infection and intra-abdominal abscess. Moreover, the occurrence of intra-abdominal fluid collections requiring intervention and postoperative ascites, hospital stay and mortality rate were similar for both groups.

Another valid question is whether, when a drain is warranted, some type of drainage is to be preferred. In a randomized trial,[21] 102 patients were allocated to have open abdominal drainage and 84 patients to receive a closed suction drain after hepatectomy. An intra-abdominal abscess was more frequently observed with open drainage (17% vs. 5%, $p<0.05$). Overall complications (37% vs. 15%, $p<0.05$), pleural effusion (31% vs. 16%, $p<0.05$), postoperative ascites (19% vs. 3%, $p<0.05$) were also more frequently noted after open drainage, while there was no difference in the incidence of haematomas or bile collections between both types of drainage.

In conclusion, there is no evidence to support routine abdominal drain use after uncomplicated liver resections. When a drain has to be used for any particular reason, a closed suction drain is to be preferred.

COLORECTAL SURGERY

There is little agreement on the prophylactic use of drains in anastomoses in elective colorectal surgery, despite many randomized clinical trials. Once anastomotic leakage occurs, it is generally agreed that drains should be used for therapeutic purposes. However, as regards prophylactic use, no such agreement exists. In large bowel resections, drainage has been used to prevent anastomotic leakage and intra-abdominal abscess formation via the removal of fluid collections, but drains in contact with the bowel anastomosis may cause erosion and impaired anastomotic healing.

In two similar meta-analyses[4,22] of six randomized controlled studies comprising 1140 colon and rectal cancer patients in total the benefit of the routine use of abdominal drains was assessed. In three studies, an open drain had been used, in two studies a closed suction drain and in one study both types of drains were used simultaneously. The incidence of clinically or radiologically detected anastomotic leakage and of surgical site infections were not statistically different between those with, and those without, an abdominal drain. Further, there was no difference in mortality, need for reoperation or extra-abdominal complications. Hence, it seems that the routine use of an abdominal drain does not seem to be indicated after large bowel resection. There is insufficient evidence to determine whether routine drainage after colonic and colorectal anastomoses prevents anastomotic and other complications.

However, the case for rectosigmoid resections with a low anastomosis below the peritoneal flexure may be different. Anastomotic leakage is one of the most serious complications of rectal cancer surgery as it is associated with high mortality, morbidity and local recurrence. Many factors influence the incidence of colorectal anastomotic leakage, including preoperative (chemo)radiotherapy, distance from the anal verge, age, gender, nutritional status and co-morbidities. The role of pelvic drainage in reducing the incidence of extraperitoneal anastomotic colorectal leakage is uncertain. In the perioperative period, blood and fluids preferentially collect in the pelvis because of its depth and its negative internal pressure. The

large empty space remaining after total mesorectal excision (TME), the absence of a peritoneal surface in the pelvic fossa and reactive tissue hyperaemia after preoperative radiotherapy are the main causes of the increased risk of extraperitoneal fluid collection. The rationale for prophylactic pelvic drainage is to allow rapid evacuation of postoperative fluid collections, thus avoiding potential contamination, whereas the risks of the use of intra-abdominal drains, which include contamination and trauma to bowel anastomosis and vessels, have been described above. Moreover, drainage allows early detection of a dehiscence and may prevent the need for additional surgical or percutaneous procedures in the case of leakage.

In a recent meta-analysis,[5] the data of three randomized controlled trials and five non-randomized comparative studies, comprising a total of 2277 patients, were analyzed regarding the benefit of routine abdominal drainage after low anterior resection of the rectosigmoid colon. In five studies, a closed suction drain had been used and, in one, an open drain, while in the remaining two studies, both types had been arbitrarily used. There were no significant differences in infection rates or mortality. However, a tendency for a lower infection rate was observed in patients without pelvic drainage, suggesting that drainage is a conduit for microbes and requires effective management in the postoperative period. The routine use of an abdominal drain resulted in a two times lower anastomotic leakage rate ($p<0.0002$) and more than three times lower rate of re-intervention, mainly because of anastomotic leakage. Notably, the subgroup analysis of randomized controlled studies only did not reveal a significant difference for these parameters between the two groups of patients.

CONCLUSIONS

An abdominal drain may be a foe instead of a friend. The routine use of abdominal drains in abdominal oncological surgery may be beneficial, but is also associated with several disadvantages. The data in the literature are often inconsistent. Since the incidence of these complications and the number of patients included in single studies are relatively low, main evidence has to be derived from meta-analyses. Three factors must be considered when analyzing the role of pelvic drainage: the type of drain (open, closed suction and irrigation-suction); the indication for placement; and the end-point for removal. The option selected in each of these factors is often at the surgeon's discretion and thus may vary, not only between different studies but also within the population of a single study. Accordingly, it is very difficult to find homogeneity and, consequently, to search concrete conclusions.

It seems that the routine use of abdominal drains in several oncological abdominal surgical procedures, including gastrectomy, hepatectomy, distal pancreatectomy and colorectal surgery, does not generally decrease the risk of surgical site infections. Only after pancreatoduodenectomy does the routine use of an abdominal drain result in a decreased risk of surgical site infections and lower mortality. The routine use of an abdominal drain after distal pancreatectomy appears to increase the pancreatic fistula rate and the overall complication rate. While for rectosigmoid resections there was a tendency for increased risk of wound infections, the routine use of abdominal drains here appears to be justified, since it decreases the risk of anastomotic leakage and re-intervention.

In emergency cases, high risk anastomosis and insufficient haemostasis placement of an abdominal drain may be indicated. In addition, surgeons often feel the need to place an intra-abdominal drain based on their intraoperative impression regarding factors such as the degree of difficulty of the surgical procedure and the level of surgical completeness, as well as their personal assessment based on their own surgical experience or possible insecurity.

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REFERENCES

1. Nitsche U, Müller TC, Späth C, et al. The evidence based dilemma of intraperitoneal drainage for pancreatic resection - a systematic review and meta-analysis. BMC 2014; 14: 76.
2. Wang Z, Chen J, Su K, Dong Z. Abdominal drainage versus no drainage post-gastrectomy for gastric cancer. Cochrane Database Syst Rev 2015: CD008788.
3. Gurusamy KS, Samraj K, Davidson BR. Routine abdominal drainage for uncomplicated liver resection. Cochrane Database Syst Rev 2007: CD006232.
4. Karliczek A, Jesus EC, Matos D, Castro AA, Atallah AN, Wiggers T. Drainage or nondrainage in elective colorectal anastomosis: a systematic review and meta-analysis. Colorectal Dis 2006; 8: 259-265.
5. Rondelli F, Bugiantella W, Vedovati MC, et al. To drain or not to drain extraperitoneal colorectal anastomosis? A systematic review and meta-analysis. Colorectal Dis 2014; 16: O35-O42.
6. Baker MS, Borchardt KA, Baker BH, Crull S. Sump tube drainage as a source of bacterial contamination. Am J Surg 1977; 133: 617-618.
7. Cerise EJ, Pierce WA, Diamond DL. Abdominal drains: their role as a source of infection following splenectomy. Ann Surg 1970; 171: 764-769.
8. Mohseni S, Talving P, Kobayashi L, et al. Closed-suction drain placement at laparotomy in isolated solid organ injury is not associated with decreased risk of deep surgical site infection. Am Surg 2012; 78: 1187-1191.
9. Pachter HL, Hofstetter SR, Spencer FC. Evolving concepts in splenic surgery: splenorrhaphy versus splenectomy and postsplenectomy drainage: experience in 105 patients. Ann Surg 1981; 194: 262-269.
10. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control 1999; 27: 97-132.
11. Dann GC, Squires MH 3rd, Postlewait LM, et al. Value of peritoneal drain placement after total gastrectomy for gastric adenocarcinoma: a multi-institutional analysis from the US Gastric Cancer Collaborative. Ann Surg Oncol 2015, Epub ahead of print.
12. Hirahara N, Matsubara T, Hayashi H, Takai K, Fujii Y, Tajima Y. Significance of prophylactic intra-abdominal drain placement after laparoscopic distal gastrectomy for gastric cancer. World J Surg Oncol 2015; 13: 181.
13. Paye F. The pancreatic stump after pancreatoduodenectomy: the "Achille's heel" revisited. J Visc Surg 2010; 147: e13-e20.
14. Stojadinovic A, Brooks A, Hoos A, Jaques DP, Conlon KC, Brennan MF. An evidence-based approach to the su rgical management of resectable pancreatic adenocarcinoma, J Am Coll Surg 2003; 196: 954-964.
15. Schmidt CM, Choi J, Powell ES, et al. Pancreatic fistula following pancreaticoduodenectomy: clinical predictors and patient outcomes. HPB Surg 2009; 2009: 404520.
16. Rondelli F, Desio M, Vedovati MC, et al. Intra-abdominal drainage after pancreatic resection: is it really necessary? A meta-analysis of short-term outcomes**.** Int J Surg 2014; 12 Suppl 1: S40-S47.
17. Peng S, Cheng Y, Yang C, et al. Prophylactic abdominal drainage for pancreatic surgery. Cochrane Database Syst Rev 2015: CD010583.
18. Van Buren G 2nd, Bloomston M, Hughes SJ, et al. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. Ann Surg 2014; 259: 605-612.
19. Bassi C, Molinari E, Malleo G, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg 2010; 252: 207-214.
20. McMillan MT, Malleo G, Bassi C, et al. Drain Management after Pancreatoduodenectomy: Reappraisal of a Prospective Randomized Trial Using Risk Stratification. J Am Coll Surg 2015; 221: 798-809.
21. Uetsuji S, Kwon AH, Komada H, Okuda Y, Imamura A, Kamiyama Y. Clinical evaluation of closed suction drainage following hepatectomy. Surg Today 1997; 27: 298-301.
22. Jesus EC, Karliczek A, Matos D, Castro AA, Atallah AN. Prophylactic anastomotic drainage for colorectal surgery. Cochrane Database Syst Rev 2004: CD002100.

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REVIEW

Infection as a cause of carcinogenesis

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ABSTRACT

Infection is recognized worldwide as a major cause of cancer. Various infectious factors are associated with the development of cancer, including viruses, bacteria and parasites. This review article is an overview on the general aspects of infections-linked tumors. The core of this text is to summarize the main infectious agents causing cancer, giving emphasis on the causal relationship between them and the variety of mechanisms they utilize to transform human cells.

KEY WORDS: infection, carcinogenesis, cancer, viruses, bacteria, parasites

INTRODUCTION

Since the beginning of the 20th century, it has been known that certain infections play a role in cancer in animals. More recently, infections with certain viruses, bacteria and parasites have been recognized as risk factors for several types of cancer in humans.[1]

Cancer is a broad term used to describe a large variety of diseases, the common feature of which is uncontrolled cell division.[2] The process of carcinogenesis consists of three major steps: initiation, promotion, and progression. The first step in carcinogenesis, initiation, is where the cellular genome undergoes mutations, creating the potential for neoplastic development. The second step, promotion, is where the initiated cells expand by self-proliferation leading to abnormal growth and further mutations. Progression, is the process through which successive changes in the neoplasm give rise to increasingly malignant sub-populations where the cells detach from the primary tumor and invade other organs and tissues, forming metastatic growths.[2]

Two classes of regulatory genes are directly involved in carcinogenesis, the oncogenes and the anti-oncogenes.[3] Oncogenes are positive regulators of carcinogenesis. In non-transformed cells, they are inactive (proto-oncogenes). Gene mutations can activate proto-oncogenes, resulting in a gain of function.[2] Anti-oncogenes or tumor suppressor genes are negative growth regulators. In normal cells, they regulate cell proliferation by checking cell cycle progression. Mutation in these genes results in a loss of gene function, which promotes carcinogenesis.[4] The two most widely studied tumor suppressor genes are the Rb gene and p53 gene. Some infections have an impact on these two types

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of genes and as a result they induce carcinogenesis.

The most important advance in oncology ever is the understanding that some cancers have specific causes, and that these causes may be identified, leading potentially to control. The causes of some cancers are infectious agents. The first indication of carcinogenic infectious agents was reported in 1911 by Peyton Rous for which he was conferred with the Nobel Prize in 1966 for his discovery on tumor inducing viruses.[5]

EPIDEMIOLOGY

Two million new cancer cases that occurred in 2008 were attributable to infections. Of the 12.7 million new cancer cases, 16.1% where infection related.[7] This percentage was higher in less developed countries (22.9%) than in more developed countries (7.4%).[6] High mortality rate of infection associated cancers has also been reported. Of the 7.5 million deaths from cancer worldwide in 2008, an estimated 1.5 million were from cancers due to infections.[6]

The main infectious agents involved in cancer are Human Papillomavirus (HPV), Hepatitis B virus (HBV) and Hepatitis C virus (HCV), and Helicobacter pylori. HPV is recognised by the World Health Organisation (WHO) as probably the primary cause of cervical carcinoma. HBV and HCV certainly contribute to hepatocellular carcinoma and Helicobacter pylori contributes to gastric carcinoma. These four examples account for a fifth or more of cancer globally. In the developed world, the proportion is less. In certain areas of the world, other infectious agents are major contributors to cancer causation - for example, in Egypt, Schistosoma haematobium and bladder cancer, and in parts of the Far East, Epstein-Barr virus (EBV) and nasopharyngeal carcinoma. Perhaps dozens of other cancers, some extremely rare and exotic ones, are associated with some sort of infection.[5]

VIRAL ONCOLOGY

A virus is a small infectious agent, made up of a small number of genes in the form of DNA or RNA surrounded by a protein coating. It must enter a living cell in order to replicate. Several viruses are considered to be linked with cancer in humans. They are the causative agents of approximately 10%–15% of human cancers worldwide.[7]

Viruses that have been linked to carcinogenesis include several DNA viruses: Human papillomavirus (HPV), hepatitis B virus (HBV), Kaposi's sarcoma herpesvirus (KSHV), Merkel cell polyomavirus (MCV), Epstein-Barr virus (EBV), as well as at least two RNA viruses: human T-lymphotropic virus-1 (HTLV-1) and the hepatitis C virus (HCV).[7] Table 1 is a synopsis of the main viruses which are associated with cancer development.[8]

Epstein–Barr virus (EBV)

EBV, also called human herpesvirus 4 (HHV-4), is a double-stranded DNA virus that belongs to the gamma subfamily of Herpesviridae. EBV is common in the oral mucosa. The oral cavity plays a vital role in the transmission of EBV – also called kissing disease. The oral mucosa has certain preferred features, it offers more efficient transmission because the virus can be dispersed in aerosols, either released by normal breathing, or more efficiently, produced upon coughing or spitting. Moreover, as enveloped viruses, the herpes family requires moisture for survival.[9]

EBV infection is lifelong. It is transmitted through the oral cavity and infects B-cells. Then it remains in a latent state in B cells. The latent virus harbored in B-cells can be reactivated when the infected B-cell responds to unrelated infections.[10] This explains why reactivation of EBV usually appears as a secondary infection.[10]

EBV, however, is known to be tumorigenic. It increases a person's risk of getting nasopharyngeal cancinoma and various forms of lymphomas.[9,11] It is primarily associated with Burkitt lymphoma and also with Hodgkin lymphoma and stomach cancer. EBV-related cancers are more common in Africa and parts of Southeast Asia. Overall, very few people who have been infected with EBV will ever develop these cancers.[1]

Table 1. Viruses associated with cancer development

Virus	Associated cancers	Host cell origin	Mechanism
HPV	Anogenital cancers, cervical cancer	Mucosa epithelium	Inhibits p53, Bak, FaDD, procaspase 8, activates caspases 8
HBV	Hepatocellular cancer	Hepatocyte	Activates caspases 3 and 8
HCV	Same as above	Same as above	Suppresses p53-mediated apoptosis
KSHV/ HHV8	Kaposi sarcoma, pleural effusion lymphoma	B and endothelial cells	Binds to p53 and inhibits p53-dependent apoptosis
HTLV	Human T cell lymphoma	T cell	Regulation of cell-cycle, NFkβ, chromatin remodeling
EBV	Burkitt lymphoma, nasopharyngeal carcinoma, Hodgkin's disease	B cell, epithelial cell and T cell	Binds Rb and promotes cell cycle progression, inhibits p53 induced apoptosis
MCV	Merkel cell carcinoma	Neuroendocrine cells	Inactivates pRb and p53

Human Papillomaviruses (HPVs)

HPVs are a group of circular, double-stranded DNA viruses that infect epithelial cells.[7] Because of their medical importance, the human papillomaviruses (HPV) have been extensively studied, and more than 100 different genotypes have been described with certain types being classified as high risk and others as low risk. High risk HPVs can cause cancerous lesions, while low risk HPVs do not.[12,13]

HPV is known to cause cervical cancer, which is the second most common cancer in women worldwide, the fourth most common cause of mortality associated with cancer in women worldwide.[14,15] It remains a leading cause of cancer-related death in women in developing countries.[17] More than 270,000 women die from cervical cancer each year, and according to 2013 data from the WHO, the developing world accounts for more than 85% of these cases.

Initial infection requires access of infectious particles to cells in the basal layer, which for some HPV types is thought to require a break in the stratified epithelium. Following infection and uncoating, it is thought that the virus maintains its genome as a low copy number episome in the basal cells of the epithelium.[12]

Some HPV-infected women can be co-infected by other viruses or bacteria, then develop cervical inflammation. The cellular proliferative and anti-apoptotic effects of inflammation, combined with low-level expression of the E6 and E7 oncogenes encoded by the episomal HPV, contribute to cervical intraepithelial neoplasia grade 1(CIN1) and may progress further to CIN2.[17] HPV can then integrate into the human genome, enabling overexpression of the E6 and E7 oncogenes, which then facilitate the transition to CIN3 and, sometimes, invasive carcinoma.[7]

The oncogenes encoded by HPV play crucial roles in carcinogenesis. Typically, the levels of E6 and E7 oncogene expression from episomal HPV16 are low. Infection with HR-HPV induces carcinogenesis through dysregulation in the expression of the viral transforming proteins E6 and E7.[12,18]

HPV16, HPV18, HPV31 and HPV33 account for 90% of all cases of cervical cancer. Among these high-risk HPVs, HPV type 16 is the most prevalent type and by itself accounts for more than 50% of all cases of cervical cancer.[19,20] Most work on HPVs has focused on the analysis of the high-risk HPV types and in particular on HPV16, which is the primary cause of cervical cancer.[12] High-risk HPV infection is also associated with several other anogenital and oropharyngeal can-

cers. It is thought to be responsible for more than 90% of anal cancers, 70% of vaginal and vulvar cancers, 60% of penile cancers and 63% of oropharyngeal cancers.[21]

BACTERIA

There is large body of evidence regarding the role of bacteria in the complex processes of carcinogenesis.[22] Research has found that certain bacteria are associated with human cancers. Their role, however, is still unclear. Convincing evidence links some species to carcinogenesis while others appear promising in the diagnosis, prevention and treatment of cancers. An overwhelming body of evidence has determined that relationships among certain bacteria and cancers exist. The bacterial mechanisms involved are as yet unclear. These gaps in knowledge make it impossible to state the exact progression of events by which specific bacteria may cause, colonize or cure cancer. Therefore, many questions remain.[23]

The following bacterial pathogens were retrieved in association with cancer: Helicobacter Pylori, Salmonella typhi, Chlamydia species, Mycobacterium tuberculosis, Schistosoma species, Tropheryma whippelii, Opisthorchis viverrini and Clonorchis sinensis.[22]

Convincing evidence has linked Helicobacter pylori with both gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma,[24-26] however other species associated with cancers include: Salmonella typhi and gallbladder cancer,[27-30] Streptococcus bovis and colon cancer[31-34] and Chlamydia pneumoniae with lung cancer.[35-37] Important mechanisms by which bacterial agents may induce carcinogenesis include chronic infection, immune evasion and immune suppression.[38]

Certain bacterial infections may evade the immune system or stimulate immune responses that contribute to carcinogenic changes through the stimulatory and mutagenic effects of cytokines released by inflammatory cells. These include reactive oxygen species (ROS),[39,40] interleukin-8,[31] cyclooxygenase-2,[41] ROS and nitric oxide.[42] Chronic stimulation of these substances, along with environmental factors such as smoking or a susceptible host, appears to contribute significantly to carcinogenesis

The bacterial species associated with cancer etiology vary; however, the infections they cause share common characteristics.[38] The time interval between acquiring the infection and cancer development is most often years or even decades. Chronic interactions between the infective agent and immune response and/or a susceptible host appear to contribute to carcinogenesis.[28,38,43,44] Preventing or treating the infection may prevent the cancer in question. Notably, the vast majority of individuals infected with a cancer-causing species will not develop cancer.[38]

Salmonella typhi and gallbladder cancer

Salmonella typhi infection highly associated with gallbladder and hepatobiliary carcinoma. The strongest epidemiological evidence of bacterial oncogenic potential, aside of Helicobacter pylori, concerns Salmonella typhi.[23]

Worldwide, annual incidence of gallbladder cancer is 17 million cases. The highest incidence of gallbladder cancer in the world is among populations of the Andean area, North American Indians, and Mexican Americans. In Europe, the highest rates are found in Poland, the Czech Republic and Slovakia.[45] This evidence supports the notion that increased susceptibility to gallbladder cancer depends on genetic factors that predispose people to gallbladder cancer either as primary factors, or secondarily as promoters by favoring the development of cholesterol gallstones. The highest mortality rates are in South America and among Mexican Americans.[46] The malignancy is three times higher among women than men in all populations.[46]

There are several risk factors for gallbladder cancer. The main associated risk factors include cholelithiasis, obesity, reproductive factors, environmental exposure to certain chemicals, congenital developmental abnormalities of the pancreatic bile-duct junction and chronic infections of the gallbladder. Among the several risk

factors for gallbladder cancer, chronic infection with Salmonella typhi is of great importance.[23,47-50]

Infection with this bacterium of typhoid, can lead to chronic bacterial carriage in the gallbladder.[22] Recent epidemiological studies have shown that those who become carriers of Salmonella typhi have 8.47 times the increased risk of developing carcinoma of the gallbladder compared with people who have had acute typhoid and have cleared the infection.[46] It is believed that chronic infection of the gallbladder can cause gallbladder carcinoma through different processes. Bacteria are able to produce b-glucuronidase, which subsequently results in deconjugation of conjugated toxins and bile acids. As a consequence, these products may acquire a potentially carcinogenic action.[51-54]

However it should be noted that according to IARC Salmonella typhi is not considered relevant to cancer development. Currently the prevention of gallbladder cancer in high risk populations depends upon the diagnosis of gallstones and removal of the gallbladder. Indeed, a strong inverse association between number of cholecystectomies and gallbladder cancer incidence and mortality rates can be found in many countries. The increase of gallbladder cancer mortality reported in Chile in the 1980s was related to decreased rates of cholecystectomies.[55] Increased rates led to the removal of gallbladders at risk, and a reduction ofgallbladder cancer incidence and mortality in Europe and the United States.[56]

Helicobacter pylori

Helicobacter pylori, is a spiral Gram-negative, flagellated microaerophilic bacterium that expresses catalase and urease, enzymes which help neutralize host responses and enable intragastric colonization.[57,58] It is one of the most prevalent infectious diseases worldwide, affecting an estimated 40–50% of the world population.[59,61] It was identified in 1982 by Australian scientists Barry Marshall and Robin Warren, who found that it was present in a person with chronic gastritis and gastric ulcers, conditions not previously believed to have a microbial cause.

The discovery of Helicobacter pylori may have been delayed by Palmer's declaration in 1954 that there were no microorganisms in the human stomach. At that time, microorganisms were believed to be unable to survive in the acidic gastric environment.[61] Thirty years have passed since Warren and Marshall's discovery of Helicobacter pylori.[57] Since then, not only peptic ulcer diseases and chronic gastritis but also non-cardia gastric cancers and MALT lymphoma have been recognized as diseases originating from Helicobacter pylori infection.[23,57.62] Helicobacter pylori has an important role in gastric carcinogenesis, since almost all non-cardiac gastric cancers develop from a background of Helicobacter pylori-infected mucosa.[63] In contrast, exposure to Helicobacter pylori appears to reduce the risk of esophageal cancer in others.[23] Helicobacter pylori infection is now known to be the main cause of peptic ulcer disease, chronic atrophic gastritis, and gastric MALT lymphoma, as well as non-cardia gastric cancer.[57]

Helicobacter pylori has been identified as a group 1 carcinogen by the World Health Organization International Agency for Research on Cancer (WHO/IARC).[58-60,64-73]

Helicobacter pylori eradication has been shown to have a prophylactic effect against gastric cancer.[59] It has been reported as an effective strategy for both the treatment of peptic ulcers and gastricmucosa-associated lymphoid tissue (MALT) lymphoma, as well as prevention of gastric cancer.[59,62,66] However, the prophylactic effect of such eradication in human beings remains controversial

Mechanisms of carcinogenesis

CagA

A fraction of Helicobacter pylori strains become more virulent by acquiring the ability to produce and secrete a protein called cytotoxin-associated gene A (CagA).[74] CagA is encoded by the cagA gene, one of 30 genes present in a 40 kp DNA segment termed the cag pathogenicity island (cag PAI).[74] CagA is a 120–145 KDa Helicobacter pylori protein that shows no significant homology

with known proteins. The size variation is due to structural diversity in its C-terminal region.[74]

During the bacterium–gastric epithelial cell interaction, Helicobacter pylori injects CagA directly into the attached cells by means of the bacterial type IV secretion apparatus.[75-78] The translocated CagA protein localizes to the inner surface of the plasma membrane and subsequently undergoes tyrosine phosphorylation in the host cells by the tyrosine kinase.[79,80] CagA may be involved in the induction of abnormal proliferation and movement of gastric epithelial cells, a cellular condition leading to altered gastric epithelial morphology and eventually causing gastritis and gastric carcinoma.[57,58]

Vac A

Vacuolatingcytotoxin A is the second-most extensively studied Helicobacter pylori virulence factor. In addition to inducing vacuolation, VacA also promotes several cellular activities, including membrane channel formation and the release of cytochrome c from mitochondria and consequent apoptosis. VacA can also specifically inhibit T-cell activation and proliferation.[81]

Oxidative stress

Oxidative stress is a state of elevated levels of ROS. In response to pathogens, the stomach induces oxidative stress, which might be related to the development of gastric organic disorders such as gastritis, gastric ulcers, and gastric cancer, as well as functional disorders such as functional dyspepsia. Helicobacter pylori plays a major role in eliciting and confronting oxidative stress in the stomach.[82] Bacterial virulence factors, such as, cytotoxin-associated gene A (CagA), cause inflammation and activate oncogenic pathways.[60] Activated neutrophils are the main source of ROS and reactive nitrogen species production in Helicobacter pylori-infected stomachs. The oxygen-derived free radicals are one of the cytotoxic factors of Helicobacter pylori-induced gastric mucosal injury. Excessive oxidative stress can damage DNA in gastric epithelial cells, indicating its possible involvement in gastric carcinogenesis.[57]

Micro RNAs

Aberrant expression of microRNAs is also reportedly linked to gastric tumorogenesis.[60] Gastric cancer arises from multiple genetic and epigenetic alterations in oncogenes, tumor-suppressor genes, cell cycle regulators, cell-adhesion molecules, and DNA repair genes. The roles of microRNAs are increasingly apparent, and aberrant expression of microRNAs may contribute to the development and progression of gastric cancer.[60] MicroRNAs (miRNAs) are post-transcriptional regulators of gene expression that are involved in development, cell proliferation, and immune responses. Recent studies have shown that some miRNAs act as tumor suppressors or oncogenes in gastric cancer.[83] Some miRNAs, including miR-146, miR-155, miR-21, miR-27a, miR-106–93-25, the miR-221–222 clusters, and the miR-200 family, are possibly involved in Helicobacter pylori infection and associated gastric cancers.[84] MiRNA expression profiling may be a powerful tool for clinical cancer diagnosis, and regulation of miRNA expression could be a novel strategy for the chemoprevention of human gastrointestinal cancers.[85]

PARASITES

There are several well-documented relationships between infections with certain parasites and the development of cancer, in particular Schistosomiasis and bladder cancer[86-90] and Opisthorchis viverrini and Clonorchis sinensis infections with cholangiocarcinoma.[91,92] The evidence associating Schistosoma haematobium infection with the development of bladder cancer is, however, far greater than that for any other parasitic infection. It has been supported by several major studies in countries in Africa and the Middle East[87-89,93-96] and more recently confirmed as definitive.[97]

Schistosoma species

Schistosoma, commonly known as bloodflukes, are parasitic flatworms responsible for a highly significant group of infections in humans.

Schistosomiasis is considered by the World Health Organization as the second most socio-economically devastating parasitic disease, with hundreds of millions infected worldwide. Schistosomiasis is now a widespread endemic disease currently found in 75 countries. It is estimated that more than 200 million people residing in rural and agricultural areas are infected and, that between 500 million and 600 million people are at risk of infection.[98]

Three schistosoma species infect humans. In each case, the infection is associated with an increase in cancer. Schistosoma mansoni infections are associated with the development of follicular lymphoma of the spleen,[99,100] Schistosoma japonicum infections with colon cancer,[101] and Schistosoma haemalobium infections with cancer of the urinary bladder.[99,102-104] Although the evidence supporting the first two associations is somewhat limited, the involvement of Schistosoma haematobium infection in bladder cancer is more strongly supported.

The major histological cell type of bladder cancer associatedwith schistosomiasis of the urinary tract is squamous cell carcinoma.[105-107] The association of bladder cancer with Schistosomiasis seems to be related to the endemicity of the parasite.[20,108] In Egypt bladder cancer is ranked first among all the malignancies in males and it accounts for 30.8% of the total cancer incidence.[109,110] Approximately 28% of the 2500 new cancer cases reported in a 4-year register in Cairo Cancer Institute, were bladder cancer cases associated with Schistosomiasis.[111] Again, from 1970 to 1981, the incidence of bladder cancer in men and women ranked first (30.8%) among 25,148 cancer cases accessed by the registry of the National Cancer Institute, Cairo, Egypt. All of these observations support an association between Schistosomiasis and bladder cancer.

In other countries, where the endemicity of schistosomiasis is also high, such as Iraq,[112] Malawi,[113] Zambia[114] and Kuwait,[115] bladder cancer was also reported to be the leading malignant disease. In contrast, in schistosome-free countries such as Germany,[116] the United States,[117] the United Kingdom[118] and Turkey,[119] bladder carcinoma ranks from the 5th to the 7th most common cancer in men and from the 7th to the 14th in women.

Mechanisms of carcinogenesis

Schistosomal infection induces chronic inflammation and irritation in the urinary bladder and is associated with increased cancer at this site.[120,121] This could facilitate changes in at least two stages of the development of the disease: first, initiation of premalignant lesions, and second, action as a promoting agent to increase the likelihood of the conversion of these lesions to the malignant state. At the stage of initiation, activated macrophages induced at the sites of inflammation are implicated in the generation of carcinogenic nitrosamines and reactive oxygen radicals that lead to DNA damage and subsequently to events such as mutations, DNA strand breaks, and sister chromatid exchanges. Inflammatory cells have also been shown to participate in the activation of other bladder carcinogens such as the aromatic amines.

Studies have attempted to identify molecular events associated with specific genes that underlie neoplastic progression in the development of Schistosomal bladder cancer. Mutations of bladder DNA have been observed in oncogenes, tumor suppressor genes, and genes associated with cell cycle control. These include the activation of H-ras,[122] inactivation of p53,[123] and inactivation of the retinoblastoma gene.[124] Since the protein products of oncogenes are known to participate directly in cell cycle processes, any alterations of these genes or their proteins can alter their function, leading to uncontrolled cell growth and ultimately to tumor formation. In particular, mutations in the tumor suppressor gene p53 have been observed more frequently in patients with Schistomiasis-associated bladder cancer than in patients with non-Schistomiasis-associated bladder cancer.

Prevention could be achieved by elimination of the parasite through education, improved hygiene, and improved conditions in living and working environments. These are the obvious solutions,

but the level of investment required for this is well beyond the resources of most of the countries where infection is endemic.[109]

CONCLUSIONS

In conclusion, nowadays there is no doubt that specific bacteria species, parasites and virus infections are associated with cancer development. The International Agency for Research on Cancer classifies microorganisms into 4 groups. Only those which belong in Group 1 are considered to be carcinogenic to humans.

Infections can raise a person's risk of cancer in different ways. Some of them, mostly viruses, directly affect the genes inside cells that control their growth by inserting their own genes into the cell, causing the cell to grow out of control. Others cause long-term inflammation that can lead to changes in the affected cells and in nearby immune cells, which can eventually lead to cancer. The microorganisms vary, but share a common characteristic: the time interval between infection and cancer development. Cancer typically takes years to decades to develop following the initial infection.

Knowledge of the etiology of infection-mediated carcinogenesis, the networking of pathways involved in the transition from infection to cancer and information on the risk factors associated with each type of cancer, all suggest prophylactic and therapeutic strategies that may reduce the risk of infection- mediated cancer.[8]

In summary, recent research has uncovered a great deal of information regarding the mechanisms used to cause or cure cancer. However, many questions remain. The detailed mechanisms of how microorganisms cause and accelerate carcinogenesis are still not fully understood and require further study.[7] It is evident, therefore, that more studies deserve to be pursued, since they may lead to measures which are equally applicable to microorganism-associated cancers and hence, are of general relevance for the understanding of neoplastic disease.

REFERENCES

1. American Cancer Society. Infections that can lead to cancer. http://www.cancer.org/cancer/cancercauses/othercarcinogens/infectiousagents/infectiousagentsandcancer/infectious-agents-and-cancer-toc. Accessed at July 2, 2015.
2. Devi PU. Basics of carcinogenesis. Health Administrator 2005; 17: 16-24.
3. Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. Nature Med 2004; 10: 789-799.
4. Perkins AS, Stern DF. Molecular biology of cancer: oncogenes. In: Cancer: Principles and practice of oncology. DeVita VD, Hellman S, Rosenberg SA (eds). 5th ed. Lippincott-Raven Publishers, Philadelphia, 1997; pages 79-105.
5. Rous P, Murphy JB, Tytler WH. The role of injury in the production of a chicken sarcoma by a filterable agent. JAMA 1912; 58: 1751.
6. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis Lancet Oncol 2012; 13: 607-615.
7. Fuentes-Gonzalez AM, Contreras-Paredes A, Manzo-Merino J, Lizano M. The modulation of apoptosis by oncogenic viruses. Virol J 2013; 10: 182.
8. Chen Y, Williams V, Filippova M, Filippov V, Duerksen-Hughes P. Viral carcinogenesis: factors inducing DNA damage and virus integration. Cancers (Basel) 2014; 6: 2155-2186.
9. Grinde B. Herpes viruses: latency and reactivation - viral strategies and host response. J Oral Microbiol 2013; 5: 10.3402/jom.v5i0.22766.
10. Odumade OA, Hogquist KA, Balfour HH, Jr. Progress and problems in understanding and managing primary Epstein-Barr virus infections. Clin Microbiol Rev 2011; 24: 193-209.
11. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. Lancet 1964; 1: 702-703.
12. Doorbar J. The papillomavirus life cycle. J Clin Virol 2005; 32: Suppl 1: S7-S15.
13. Ault KA. Human papillomavirus vaccines and the potential for cross-protection between related HPV types. Gynecol Oncol 2007; 107: S31-S33.
14. Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine 2006; 24: S3/11-S3/25.
15. World Health Organization. Cancers of the female reproductive organs. In: World cancer report 2014.

Stewart BW, Wild CP (eds). IARC, Lyon, France, 2014; pages 465-481.
16. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999; 189: 12-19.
17. Williams VM, Filippova M, Soto U, Duerksen-Hughes PJ. HPV-DNA integration and carcinogenesis: Putative roles for inflammation and oxidative stress. Future Virol 2011; 6: 45-57.
18. Stunkel W, Bernard HU. The chromatin structure of the long control region of human papillomavirus type 16 represses viral oncoprotein expression. J Virol 1999; 73: 1918-1930.
19. Liu, Y, Tergaonkar, V, Krishna, S, Androphy, EJ. Human papillomavirus type 16 E6-enhanced susceptibility of l929 cells to tumor necrosis factor alpha correlates with increased accumulation of reactive oxygen species. J Biol Chem 1999; 274: 24819-24827.
20. Lowy DR, Kirnbauer R, Schiller JT. Genital human papillomavirus infection. Proc Natl Acad Sci USA 1994; 91: 2436-2440.
21. Wu XC, Watson M, Wilson R, Saraiya M, Cleveland JL, Markowitz L. Human Papillomavirus-Associated Cancers-United States, 2004-2008. MMWR Morb Mortal Wkly Rep 2012; 61: 258-261.
22. Samaras V, Rafailidis PI, Mourtzoukou EG, Peppas G, Falagas ME. Chronic bacterial and parasitic infections and cancer: a review J Infect Dev Ctries 2010; 4: 267-281.
23. Mager DL. Bacteria and cancer: cause, coincidence or cure? A review. J Transl Med 2006; 4: 14.
24. Crowe SE. Helicobacter infection, chronic inflammation, and the development of malignancy. Curr Opin Gastroenterol 2005; 1: 32-38.
25. Montalban C, Santon A, Boixeda D, Bellas C. Regression of gastric high grade mucosa associated lymphoid tissue (MALT) lymphoma after Helicobacter pylori eradication. Gut 2001; 49: 584-587.
26. Persing DH, Prendergast FG. Infection, immunity, and cancer. Arch Pathol Lab Med 1999; 123: 1015-1022.
27. Vaishnavi C, Kochhar R, Singh G, Kumar S, Singh S, Singh K. Epidemiology of typhoid carriers among blood donors and patients with biliary, gastrointestinal and other related diseases. MicrobiolImmunol 2005; 49: 107-112.
28. Lax AJ, Thomas W. How bacteria could cause cancer: one step at a time. Trends Microbiol 2002; 10: 293-299.
29. Dutta U, Garg PK, Kumar R, Tandon RK. Typhoid carriers among patients with gallstones are at increased risk for carcinoma of the gallbladder. Am J Gastroenterol 2000; 95: 784-787.
30. Shukla VK, Singh H, Pandey M, Upadhyay SK, Nath G. Carcinoma of the gallbladder – is it a sequel of typhoid? Dig Dis Sci 2000; 45: 900-903.
31. Biarc J, Nguyen IS, Pini A, et al. Carcinogenic properties of proteins with pro-inflammatory activity from Streptococcus infantarius (formerly S. bovis). Carcinogenesis 2004; 25: 1477-1484.
32. Gold JS, Bayar S, Salem RR. Association of Streptococcus bovis bacteremia with colonic neoplasia and extracolonic malignancy. Arch Surg 2004; 139: 760-765.
33. Ellmerich S, Scholler M, Duranton B, et al. Promotion of intestinal carcinogenesis by Streptococcus bovis. Carcinogenesis 2000; 21: 753-756.
34. Zarkin BA, Lillemoe KD, Cameron JL, Effron PN, Magnuson TH, Pitt HA. The triad of Streptococcus bovis bacteremia, colonic pathology, and liver disease. Ann Surg 1990; 211: 786-791.
35. Littman AJ, White E, Jackson LA, et al. Chlamydia pneumoniae infection and risk of lung cancer. Cancer Epidemiol Biomarkers Prev 2004; 13: 1624-1630.
36. Koyi H, Branden E, Gnarpe J, Gnarpe H, Steen B. An association between chronic infection with Chlamydia pneumoniae and lung cancer. A prospective 2-year study. APMIS 2001; 109: 572-580.
37. Anttila T, Koskela P, Leinonen M, et al. Chlamydia pneumoniae infection and the risk of female early-onset lung cancer. Int J Cancer 2003; 107: 681-682.
38. Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. J Intern Med 2000; 248: 171-183.
39. Schoppmann SF, Birner P, Stockl J, et al. Tumor-associated macrophages express lymphatic endothelial growth factors and are related to peritumorallymphangiogenesis. Am J Pathol 2002; 161: 947-956.
40. Baik SC, Youn HS, Chung MH, et al. Increased oxidative DNA damage in Helicobacter pylori infected human gastric mucosa. Cancer Res 1996; 56: 1279-1282.
41. Sheng H, Shao J, Washington MK, DuBois RN. Prostaglandin E2 increases growth and motility of colorectal carcinoma cells. J Biol Chem 2001; 276: 18075-18081.
42. Mannick EE, Bravo LE, Zarama G, et al. Inducible nitric oxide synthase, nitrotyrosine and apoptosis

in Helicobacter pylori gastritis: effects of antibiotics and antioxidants. Cancer Res 1996; 56: 3238-3243.
43. Ries LAG, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review, 1975-2002. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/archive/csr/1975_2002/. Accessed July 15, 2015.
44. Correa P, Miller MJ. Carcinogenesis, apoptosis and cell proliferation. Br Med Bull 1998; 54: 151-162.
45. Miquel JF, Covarrubias C, Villaroel L, et al. Genetic epidemiology of cholesterol cholelithiasis among Chilean Hispanics, Amerindians, and Maoris. Gastroenterology 1998; 115: 937-946.
46. Lazcano-Ponce EC, Miquel JF, Munoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 2001; 51: 349-364.
47. Wistuba II, Gazdar AF. Gallbladder cancer: lessons from a rare tumour. Nat Rev Cancer 2004; 4: 695-706.
48. Lazcano-Ponce EC, Miquel JF, Munoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 2001; 51: 349-364.
49. Kumar S, Kumar S, Kumar S. Infection as a risk factor for gallbladder cancer. J Surg Oncol 2006; 93: 633-639.
50. Wistuba II, Gazdar AF. Gallbladder cancer: lessons from a rare tumour. Nat Rev Cancer 2004; 4: 695-706.
51. Levin B. Gallbladder carcinoma. Ann Oncol 1999; 10: Suppl 4: 129-130.
52. Chipman JK. Bile as a source of potential reactive metabolites. Toxicology 1982; 25: 99-111.
53. Mackowiak PA. Microbial oncogenesis. Am J Med 1987; 82: 79-97.
54. Hill MJ. Chronic bacterial infection and subsequent human carcinogenesis. Eur J Cancer Prev 1995; 4: 127-128.
55. Chianale J, Del Pino G, Nervi F. Increasing gallbladder cancer mortality rate during the last decade in Chile, a high-risk area. Int J Cancer 1990; 46: 1131-1133.
56. Wood R, Fraser LA, Brewster DH, Garden OJ. Epidemiology of gallbladder cancer and trends in cholecystectomy rates in Scotland, 1968–1998. Eur J Cancer 2003; 39: 2080-2086.
57. Suzuki H, Nishizawa T, Tsugawa H, Hibi T. Molecular approaches and modern clinical strategies for the management of Helicobacter pylori infection in Japan. Keio J Med 2012; 61: 109-119.
58. Higashi H, Tsutsumi R, Fujita A, et al. Proc Natl Acad Scie U S A 2002; 99: 14428-14433
59. Suzuki H, Nishizawa T, Hibi T. Helicobacter pylori eradication therapy. Future Microbiol 2010; 5: 639-648.
60. Nishizawa T, Suzuki H. Gastric carcinogenesis and underlying molecular mechanisms: Helicobacter pylori and novel targeted therapy. Biomed Res Int 2015; 2015: 794378.
61. Palmer ED. Investigation of the gastric mucosa spirochetes of the human. Gastroenterology 1954; 27: 218-220.
62. Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 2008; 372: 392-397.
63. Uemura N, Okamoto S, Yamamoto S, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 2001; 345: 784-789.
64. Forman D, Newell DG, Fullerton F, et al. Association between infection with Helicobacter pylori and risk of gastric cancer. BMJ 1991; 302: 1302-1305.
65. Nomura A, Stemmermann GN, Chyou P, et al. Helicobacter pylori infection and gastric carcinoma among Japanese Americans in Hawaii. N Engl J Med 1991; 325: 1132-36.
66. Parsonnet J, Friedman GD, Vandersteen DP, et al. Helicobacter pylori infection and risk of gastric carcinoma. N Engl J Med 1991; 325: 1127-1131.
67. Huang JQ, Sridhar S, Chen Y, et al. Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer. Gastroenterology 1998; 114: 1169-1179.
68. Danesh J. Helicobacter pylori infection and gastric cancer: systematic review of the epidemiological studies. Aliment Pharmacol Ther 1999; 13: 851-856.
69. Eslick GD, Lim LL, Byles JE, et al. Association of Helicobacter pylori infection with gastric carcinoma: a meta-analysis. Am J Gastroenterol 1999; 94: 2373-2379.
70. Asaka M, Kimura T, Kato M, et al. Possible role of Helicobacter pylori infection in early gastric cancer development. Cancer 1994; 73: 2691-2694.
71. Kikuchi S, Wada O, Miki K, et al. Serum pepsinogen as a new marker for gastric carcinoma among young adults. Cancer 1995; 75: 2789-2793.
72. World Health Organization International Agency for Research on Cancer. Schistosomes, liver flukes and Helicobacter pylori. Lyon: IARC, 1994.
73. Nishizawa T, Suzuki H, Nakagawa I, et al. Early Heli-

cobacter pylori eradication restores sonic hedgehog expression in the gastric mucosa of mongolian gerbils. Digestion 2009; 79: 99-108.
74. Hatakeyama M. Oncogenic mechanisms of the Helicobacter pylori CagA protein. Nat Rev Cancer 2004; 4: 688-694.
75. Asahi M, Azuma T, Ito S, et al. Helicobacter pylori CagA protein can be tyrosine phosphorylated in gastric epithelial cells. J Exp Med 2000; 191: 593-602.
76. Stein M, Rappuoli R, Covacci A. Tyrosine phosphorylation of the Helicobacter pylori CagA antigen after cag-driven host cell translocation Proc Natl Acad Sci U S A 2000; 97: 1263-1268.
77. Odenbreit S, Puls J, Sedlmaier B, Gerland E, Fischer W, Haas R. Translocation of Helicobacter pylori CagA into gastric epithelial cells by type IV secretion. Science 2000; 287: 1497-1500.
78. Backert S, Ziska E, Brinkmann V, et al. Translocation of the Helicobacter pylori CagA protein in gastric epithelial cells by a type IV secretion apparatus. Cell Microbiol 2000; 2: 155-164.
79. Stein M, Bagnoli F, Halenbeck R, Rappuoli R, Fantl WJ, Covacci A. c-Src/Lyn kinases activate Helicobacter pylori CagA through tyrosine phosphorylation of the EPIYA motifs. Mol Microbiol 2002; 43: 971-980.
80. Selbach M, Moese S, Hauck CR, Meyer T F, Backert S. Src is the kinase of the Helicobacter pylori CagA protein in vitro and in vivo. J Biol Chem 2002; 277: 6775-6778.
81. Yamaoka Y. Mechanisms of disease: Helicobacter pylori virulence factors. Nat Rev Gastroenterol Hepatol 2010; 7: 629-641.
82. Suzuki H, Nishizawa T, Tsugawa H, Mogami S, Hibi T. J Clin Biochem Nutrn 2012; 50: 35-39.
83. Saito Y, Suzuki H, Tsugawa H, et al. Chromatin remodeling at Alu repeats by epigenetic treatment activates silenced microRNA-512-5p with downregulation of Mcl-1 in human gastric cancer cells. Oncogene 2009; 28: 2738-2744
84. Belair C, Darfeuille F, Staedel C. Helicobacter pylori and gastric cancer: possible role of microRNAs in this intimate relationship. Clin Microbiol Infect 2009; 15: 806-812.
85. Saito Y, Suzuki H, Hibi T. The role of microRNAs in gastrointestinal cancers. J Gastroenterol 2009; 44 Suppl 19: 18-22.
86. Badawi AF, Cooper, DP, Mostafa MH, et al. Promutagenic methylation damage in liver DNA of mice infected with Schistosoma mansoni. Carcinogenesis 1993; 14: 653-657.
87. Badawi AF, Mostafa MH, O'Connor PJ. Involvement of alkylating agents in schistosome-associated bladder cancer: the possible basic mechanisms of induction. Cancer Lett 1992 63: 171-188.
88. Badawi AF, Mostafa MH, Aboul-Asm T, Haboubi NY, O'Connor PJ, Cooper DP. Promutagenic methylation damage in bladder DNA from patients with bladder cancer associated with schistosomiasis and from normal individuals. Carcinogenesis 1992; 13: 877-881.
89. Schwartz DA. 1981. Helminths in the induction of cancer. II. Schistosoma haematobium and bladder cancer. Trop Geogr Med 1981; 33: 1-7.
90. Tricker AR, Mostafa MH, Spiegelhalder B, Preussmann R. Urinary excretion of nitrate, nitrite and N-nitroso compounds in schistosomiasis and bilharzial bladder cancer patients. Carcinogenesis 1989; 10: 547-552.
91. Hou PC. The relationship between primary carcinoma of the liver and infestation with Clonorchissinensis. J Pathol Bacteriol 1956; 72: 239-246.
92. Srivatanakul P, Oshima H, Khlat M, et al. Opisthorchis viverrini infestation and endoxgenous nitrosamines as risk factors for cholangiocarcinoma in Thailand. Int J Cancer 1991; 48: 821-825.
93. Cheever AW. Schistosomiasis and neoplasia. J Natl Cancer Inst 1978; 61: 13-18.
94. Chen MG, Mott KE. Progress in the assessment of morbidity due to Shistosoma haematobium infections: a review of the recent literature. Trop Dis Bull 1989; 48: 2643-2648.
95. Hashem M, Boutros K. The influence of bilharzial infection on the carcinogenesis of the bladder. An experimental study. J Egypt Med Assoc 1961; 44: 598-606.
96. Mostafa MH, Helmi S, Badawi AF, Tricker AR, Spiegelhalder B, Preussman R. Nitrate, nitrate and volatile N-nitroso compounds in the urine of Schistosoma mansoni infected patients. Carcinogenesis 1994; 15: 619-625.
97. World Health Organization. Evaluation of carcinogenic risk to humans. Schistosomes, liver flukes and Helicobacter pylori. IARC Monogr 1994; 61: 45-119.
98. Wild D, Feser W, Michel S, Lord HL, Josephy PD. Metabolic activation of heterocyclic aromatic amines by human arylamineNacetyltransferase isoenzymes (NAT1 and NAT2) expressed in Salmonella typhimu-

rium. Carcinogenesis 1995; 16: 643-648.
99. World Health Organization. The control of schistosomiasis. Report of a WHO Expert Committee. WHO Tech Rep Ser 1985: 728.
100. Andrade ZA, Abreu WN. Follicular lymphoma of the spleen in patients with hepatosplenic Schistosomiasis mansoni. Am J Trop Med Hyg 1971; 27: 237-243.
101. Chen M, Molt K. Progress in assessment of morbidity due to Schistosoma japonicum infection. Trop Dis Bull 1988, SS: 2056.
102. Chen M, Molt K. Progress in assessment of morbidity due to Schistosoma haematohium infection. Trop Dis Bull 1989; 86: 2-36.
103. Tawfik HN. Carcinoma of the urinary bladder associated with schistosomiasis in Egypt: the possible causal relationship. In: Unusual Occurrences as Clues to Cancer Etiology. Miller RW (ed.). Japanese Science Society Press, Tokyo, 1988; pages 197-209.
104. World Health Organization. Progress in assessment of morbidity due to Schistosoma haematobium infection. A review of recent literature. WHO Tech Rep Ser 1987; 87. 91.
105. Khurana P, Morad N, Khan AR, Shetty S, Ibrahim A, Patil K. Impact of schistosomiasis of urinary bladder cancer in the southern province of Saudi Arabia: review of 60 cases. J Trop Med Hyg 1992; 95: 149-151.
106. Koraitim NM, Metwalli NE, Atta MA, El-Sadr AA. Changing age incidence and pathological types of Schistosoma-associated bladder carcinoma. J Urol 1995; 154: 1714-1716.
107. Koroltchouk V, Stanley K, Stjernsward J, Mott K. Bladder cancer: approaches to prevention and control. Bull W H O 1987; 65: 513-520.
108. Mostafa MH, Sheweita SA, O'Connor PJ. Relationship between schistosomiasis and bladder cancer. Clin Microbiol Rev 1999; 12: 97-111.
109. Ibrahim AS. Site distribution of cancer in Egypt: twelve years experience (1970–1981). In: Cancer prevention in developing countries. Khogali M, Omar YT, Gjorgov A, Ismail AS (eds). Pergamon Press, Oxford, United Kingdom, 1986; pages 45-50.
110. Kahan E, Ibrahim AS, El Najjar K, et al. Cancer patterns in the Middle East. Special report from the Middle East Cancer Society. Acta Oncol 1997; 36: 631-636.
111. El-Sebai I. Parasites in the etiology of cancer; bilharziasis and bladder cancer. CA Cancer J Clin 1997; 27: 100-106.
112. Al-Saleem T, Alsh N, Tawfikh LE. Bladder cancer in Iraq: the histological subtypes and their relationship to schistosomiasis. Ann Saudi Med 1990; 10: 161-164.
113. Lucas SB. Squamous cell carcinoma of the bladder and schistosomiasis. East Afr Med J 1982; 59: 345-351.
114. Elem B, Purohit R. Carcinoma of urinary bladder in Zambia: a quantitative estimate of Schistosoma haematobium infection. Br J Urol 1983; 55: 275-278.
115. Al-Shukri SM, Alwan H, Nayef M, Rahman AA. Bilharsiasis in malignant tumors of the urinary bladder. Br J Urol 1987; 59: 59-62.
116. Becker N, Beyme RF, Wagner G. Atlas of cancer mortality in the Federal Republic of Germany. Springer-Verlag KG, Berlin, Germany, 1984.
117. Deves SS, Silverman DT, Young JL. Cancer incidence and mortality trends among whites in the United States, 1947–84. J Natl Cancer Inst 1987; 79: 701-770.
118. Office of Population Censuses and Surveys. Cancer statistics registrations: England and Wales. Government Statistical Services. HMSO, London, United Kingdom, 1983.
119. Bilir N. Turkey: National histopathological survey, 1977. IARC Sci Publ 1986; 75: 303-307.
120. Rosin MP, Anwar WA, Ward AJ. Inflammation, chromosomal instability and cancer: the schistosomiasis model. Cancer Res 1994; 54: Suppl 7: 1929s-1933s.
121. Rosin MP, El-Din SS, Ward AJ, Anwar WA. Involvement of inflammatory reactions and elevated cell proliferation in the development of bladder cancer in schistosomiasis patients. Mutat Res 1994; 305: 283-292.
122. Knowles MA, Williamso M. Mutation of H-ras is infrequent in bladder cancer: confirmation by single-strand-conformation-polymorphism analysis, designed restriction-fragment-length polymorphisms, and direct sequencing. Cancer Res 1993; 53: 133-139.
123. Sidransky D, Von Eschenbach A, Tsai YC, et al. Identification of the p53 gene mutations in bladder cancers and urine samples. Science 1991; 252: 706-709.
124. Ishikawa J, Xu HJ, Hu XS, et al. Inactivation of the retinoblastoma gene in human bladder and renal-cell carcinomas. Cancer Res 1991; 51: 5736-5743.

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REVIEW

Surgical infection and cancer recurrence

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ABSTRACT

Surgical infection is an integral part of surgical practice. The latest research findings reinforce the view that the surgical site infection in cancer patients increases the likelihood of recurrence and reduces overall and relapse-free survival. Strong evidence exists that this is the case for breast cancer, gastric cancer and colorectal cancer. At the moment, there are no data that suggest an adverse effect of surgical site infections on oncologic outcome for cutaneous melanoma and soft tissue sarcoma. Continuing education and training of surgeons leading to improved surgical technique and postoperative care are indispensable in reducing the risk of surgical site infections and to avoid their adverse effect on survival.

KEY WORDS: surgical site infection, cancer recurrence

INTRODUCTION

Surgical infection is an integral part of surgery and requires daily involvement of the surgeon. The aim of the present review of the current literature is to seek evidence of the adverse effect of this common complication of surgery on oncologic outcome. Surgical site infections are the most common nosocomial infections in surgical patients, contributing to perioperative morbidity, prolonged postoperative hospital length of stay, and increased hospital costs. Surgical site infections can be superficial incisional, deep incisional and organ/space surgical site infections (Table 1).[1]

In surgical oncology patients, cancer itself, the operation for cancer treatment and other factors such as age, body mass index, diabetes, smoking, nutrition, anaemia and stage of cancer predispose these patients to more frequent occurrence of surgical infections.[2]

In cancer patients, surgical site infections generally occur as a complication of the surgical treatment of solid tumours. The question that arises is whether surgical site infection increases the oncological burden of the patient and, if there is such a possibility, how it affects cancer recurrence. Since the solid tumours that are most frequently encountered in daily practice are breast, gastric, pancreatic and colorectal cancer, as well as cutaneous melanoma and soft tissue sarcomas, a literature search is performed for data of each of these tumour types regarding the effect of surgi-

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Table 1. Classification and definition of a surgical site infection.1

Superficial incisional surgical site infection
Infection within 30 days after the operation, only involves skin and subcutaneous tissue of the incision, and at least one of the following:
1. Purulent drainage with or without laboratory confirmation from the superficial incision
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial tissue
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat; and superficial incision is deliberately opened by surgeon, unless incision is culture-negative
4. Diagnosis of superficial incisional surgical site infection made by a surgeon or attending physician
Deep incisional surgical site infection
Infection within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissue (e.g. fascia, muscle) of the incision and at least one of the following:
1. Purulent drainage from the deep incision, but not from the organ/space component of the surgical site
2. A deep incision spontaneously dehisces or is deliberately opened by surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain or tenderness, unless incision is culture-negative
3. An abscess or other evidence of infection involving the deep incision that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of deep incisional surgical site infection made by a surgeon or attending physician
Organ/space surgical site infection
Infection within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (e.g. organs and spaces) other than the incision, which was opened or manipulated during an operation and at least one of the following:
1. Purulent drainage from a drain that is placed through a stab wound into the organ/space
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of organ/space surgical site infection made by a surgeon or attending physician

cal site infection on the oncologic burden and, subsequently, on the oncologic outcome

The term 'oncologic burden' means the increase in cancer load of the patient, either microscopically (cells) or macroscopically (local recurrence, distant metastasis - lymphatic and / or haematogenous). The oncologic burden could be empirically classified into direct and indirect burden, and short and long-term burden. While the indirect oncologic burden is the one caused by the delay of adjuvant treatment (chemotherapy and/or radiotherapy) due to complications such as surgical infection, the direct oncologic burden concerns the direct effect of surgical site infections to the cancer load of the patient. Short-term oncologic burden refers to the immediate postoperative period (1-3 months after surgery), while the long-term burden refers to the ultimate postoperative period.

BREAST CANCER

Breast surgery is considered clean surgery. Nevertheless, there are surgical infections at the following rates: 2.3% after excisional biopsy, 6.6%

after lumpectomy and sentinel lymph node biopsy or/and axillary lymph node dissection, and 19% after mastectomy with or without axillary lymphadenectomy. Such infections are superficial surgical site infections. The microorganisms most commonly responsible for these infections are Streptococci species, Staphylococcus Aureus and coagulase-negative Staphylococci.[3]

The increased research interest in this matter led to a retrospective study of 1065 patients who had undergone surgery for breast cancer from 1994 to 2001.[4] Nine per cent of the patients had experienced a surgical wound infection. The results of this study suggest that delayed wound healing is associated with increased incidence of systemic relapse following surgery for breast cancer. In all groups of patients the risk of systemic relapse increased after infection of the wound. Among patients at high risk for distant metastases after initial treatment, those with wound complications had a significantly lower 5-year systemic recurrence-free survival than those without wound complications (29.3% vs. 57.3%, p<0.001). The difference was smaller, but still significant, for patients at intermediate and low risk (70.5% vs. 87.3%, p=0.002 and 88.9% vs. 96.2%, p=0.02, respectively). The pathogenetic mechanism is not clear, but it might be that IL-6, TNF-α and angiogenic factors play a role.

GASTRIC CANCER

Thirteen per cent of the patients who undergo an operation for a malignancy of the gastrointestinal tract present a surgical site infection in the postoperative period. Four per cent of these infections refer to an anastomotic leakage.[3]

In gastric cancer patients, it seems that postoperative infectious complications are associated with an increased risk of disease recurrence. In a small retrospective Japanese study,[5] the only independent prognostic factor for early hepatic recurrence of gastric cancer was postoperative infection. In a large series of 765 Japanese patients who underwent curative gastrectomy for gastric cancer,[6] 81 patients (10.6%) had intra-abdominal infectious complications. Forty-two patients (5.5%) had pancreas-related infectious complications, 18 (2.4%) an anastomotic leakage and 21 (2.7%) an intra-abdominal abscess. Intra-abdominal infections were more frequently seen after a total gastrectomy, in more advanced disease, after D2 lymphadenectomy and when splenectomy concurrently was performed. The 5-year overall and relapse-free survival was worse in the group of patients with an intra-abdominal infection (66.4% vs. 86.8%, p<0.001 and 64.9% vs. 84.5%, p<0.001, respectively). This trend was still observed after stratification by pathological stage. For stage II disease the 5-year overall and relapse-free survival rates were 63.0% vs. 81.1% (p=0.02) and 55.6% vs. 78.0% (p=0.02), respectively, and for stage III disease 40.5% vs. 63.3% (p=0.03) and 41.3% vs. 55.1% (p=0.11). The last difference did most probably not reach statistical significance because of the small number of stage III patients (21) with an intra-abdominal infection in the study. In a multivariate analysis, the occurrence of an intra-abdominal infection was associated with a more than two-fold decrease of overall and relapse-free survival in patients with gastric cancer.

It is unclear why postoperative intra-abdominal infectious complications affect the long-term outcome of patients. It is hypothesized that patients with intra-abdominal infections have severe immune suppression resulting in high recurrence rates and poor overall and relapse-free survival rates.[6] Specifically, cell-mediated immunity, involving natural killer cells and cytotoxic T lymphocytes in particular, is compromised, and the degree of suppression is considered to be related to the extent of surgical trauma and tissue damage. Postoperative intra-abdominal infections increase surgical stress and cause severe tissue damage due to local and generalized inflammatory reactions, resulting in more severe immune suppression and possibly leading to promotion of

metastatic growth and an increased risk of early disease recurrence. This hypothesis should be tested by assessing the degree of immune suppression during surgical site infections and the relation to disease recurrence. Since in the above study[6] the incidence of local recurrence did not increase after anastomotic leakage, implantation of cancer cells into the abdominal cavity does not seem to be a contributing factor in gastric cancer.

COLORECTAL CANCER

In colorectal cancer, the data are even more convincing regarding the association of postoperative infectious complications and long-term cancer-specific outcome. Over a long period, various research groups[7-9] have observed that local recurrence occurs more frequently after surgical infection.

Most recently, large databases were analysed to define the association of postoperative infections and long-term oncologic outcome.[10] The overall morbidity and infectious complication rates were 27.8% and 22.5%, respectively, in 12,075 patients who underwent resection for non-metastatic colorectal cancer. The presence of any complication was independently associated with decreased long-term survival, but multivariate analysis by complication type demonstrated increased risk of death from colorectal cancer only with infectious complications (1.3-fold risk). This effect is predominantly seen in patients with severe infections. Various explanations for this association were proposed: 1) an increase of cytokines and inflammatory mediators which leads to promotion of metastatic growth, 2) correlation of increased risk of surgical infection with advanced disease, 3) delayed initiation of adjuvant therapy due to complications, 4) intraluminal escape of tumour cells in the case of anastomotic leakage, and 5) poor surgical technique which can increase the recurrence and the infectious complications.

In a mice model,[11] postoperative surgical site infection increased angiogenesis and tumour recurrence after surgical excision of colon cancer. In a recent prospective matched cohort study,[12] thirty patients who had an anastomotic leak or intra-abdominal abscess were included and matched with patients who had an uncomplicated post-operative course. IL-6 and VEGF were measured in serum and peritoneal fluid. The patients with an intra-abdominal infection following surgery for colorectal cancer exhibited increased levels of IL-6 and VEGF, and displayed a higher 2-year recurrence rate (30% vs. 4%, p=0.001) Hence, the amplification of inflammation and angiogenesis may be one of the mechanisms responsible for the increased incidence of disease relapse in patients with anastomotic leakage or intra-abdominal abscess.

CUTANEOUS MELANOMA AND SARCOMA

After lymph node dissection, especially in the groin, wound infections and other complications are frequently observed. In a small recent study,[13] wound infection after melanoma surgery was not associated with an increased risk of disease recurrence.

Conflicting results have been reported as to whether postoperative infection may even confer a survival benefit after osteosarcoma resection. In a retrospective series of 412 surgically treated osteosarcoma patients,[14] 41 of the patients (10%) displayed an early deep wound infection. These patients had significantly better survival and infection was an independent prognostic factor on Cox regression analysis. This survival benefit was not confirmed in a recent study,[15] in which oncological outcome of 31 osteosarcoma patients with deep wound infections was compared with that of 316 non-infected patients. Although overall and metastasis-free survival rates for the 31 infected patients were very high, no survival difference was noted between infected and non-infected patients after matching for clinical factors. This study suggests that the previously reported posi-

tive effect on survival is likely to be related to the clinical characteristics of infected patients rather than on an antitumour effect due to the infection.

Postoperative infection after resection of a primary soft tissue sarcoma is a major complication with both local and systemic implications for patients. The estimated incidence of infection is 5-13% and can range in severity from cellulitis and wound breakdown to complete loss of a limb and even sepsis. Postoperative infection may also delay critical adjuvant treatment such as chemotherapy or local radiation therapy; this delay in multi-modality treatment has the potential to negatively affect rates of recurrence, metastasis or even disease-specific death. In a retrospective study of 396 patients treated surgically for soft tissue sarcoma,[16] oncologic data of 56 patients with postoperative wound infection were compared with those of matched patients who did not. In these balanced cohorts, there was no difference in survival, local recurrence or metastasis between patients with, or without, a postoperative infection. Hence, postoperative infection neither conferred a protective effect, nor increased the risk of adverse oncologic outcomes after soft tissue sarcoma resection.

CONCLUSIONS

The increase of oncologic burden after surgical infection began as a hypothesis under investigation, but seems to be established as a fact in clinical practice. However the pathogenetic mechanism leading to it is not yet clear. In some solid tumours, surgical site infection may adversely affect the overall and relapse-free survival. From us, as surgeons, the continuous improvement of the surgical technique and post-operative care of patients is required in order to reduce surgical infections and their complications for patients.[17] Surgeons have to perform their operations with meticulous care in order to decrease the surgical site infection rate and to consequently improve the long-term outcome of cancer patients.

REFERENCES

1. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: A modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 1992; 13: 606–608.
2. Ishikawa K, Kusumi T, Hosokawa M, et al. Incisional surgical site infection after elective open surgery for colorectal cancer. Int J Surg Oncol 2014: 419712.
3. Sutton SH. Infections associated with solid malignancies. In: Infectious complications in cancer patients. Stosor V, Zembower TR (eds). Springer, Cham, Switzerland, 2014; pages 371-411.
4. Murthy BL, Thomson CS, Dodwell D, et al. Postoperative wound complications and systemic recurrence in breast cancer. Br j Cancer 2007; 97: 1211–1217.
5. Ohtsuka T, Kitajima Y, Takahashi T, et al. Infectious complications after gastric cancer surgery accelerate a rapid hepatic recurrence. Hepatogastroenterology 2009; 56: 1277-1280.
6. Tokunaga M, Tanizawa Y, Bando E, Kawamura T, Terashima M. Poor survival rate in patients with postoperative intra-abdominal infectious complications following curative gastrectomy for gastric cancer. Ann Surg Oncol 2013; 20: 1575-1583.
7. Fucini C, Bandettini L, D'Elia M, Filipponi F, Herd-Smith A. Are postoperative fever and/or septic complications prognostic factors in colorectal cancer resected for cure? Dis Colon Rectum 1985; 28: 94-95.
8. Sauven P, Playforth MJ, Evans M, Pollock AV. Early infective complications and late recurrent cancer in stapled colonic anastomoses. Dis Colon Rectum 1989; 32: 33-35.
9. Kressner U, Graf W, Mahteme H, Påhlman L, Glimelius B. Septic complications and prognosis after surgery for rectal cancer. Dis Colon Rectum 2002; 45: 316-321.
10. Artinyan A, Orcutt S, Anaya D, Richardson P, Chen J, Berger D. Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer. A study of 12.075 patients. Ann Surg 2015; 261: 497-505.
11. Bohle B, Pera M, Pascual M, et al. Postoperative intra-abdominal infection increases angiogenesis and tumor recurrence after surgical excision of colon cancer in mice. Surgery 2010; 147: 120-126.
12. Alonso S, Pascual M, Salvans S, et al. Postoperative intra-abdominal infection and colorectal cancer

recurrence: a prospective matched cohort study of inflammatory and angiogenic responses as mechanisms involved in this association. Eur J Surg Oncol 2015; 41: 208-214.
13. Ahmed A, Sadadcharam G, Huisma F, et al. Postoperative complications following nodal dissection and their association with melanoma recurrence. ISRN Surgery 2013: 382138.
14. Jeys L, Grimer R, Carter S, Tillman RM, Abudu Al. Postoperative infection and increased survival in osteosarcoma patients: Are they associated? Ann Surg Oncol 2007; 14: 2887-2895.
15. Lee J, Kim M, Kim D, et al. Postoperative infection and survival in osteosarcoma patients. Ann Surg Oncol 2009; 16: 147-151.
16. Behnke NK, Alamanda VK, Song Y. Does postoperative infection after soft tissue sarcoma resection affect oncologic outcomes? J Surg Oncol 2014; 109: 415-420.
17. Poggio JL. Perioperative strategies to prevent surgical-site infection. Clin Colon Rectal Surg 2013; 26: 168–173.

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ORIGINAL PAPER

Cytoreductive surgery and perioperative intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis from rectal cancer

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ABSTRACT

Aim: The long-term results of rectal cancer with peritoneal carcinomatosis have been controversial. The purpose of the study is the presentation of the results of cytoreductive surgery and perioperative intraperitoneal chemotherapy in patients with rectal cancer and peritoneal carcinomatosis. Material and Methods: From 2005-2014, ten patients with peritoneal carcinomatosis of rectal origin underwent cytoreductive surgery with perioperative intraperitoneal chemotherapy. Clinical indicators were correlated to survival, recurrences, morbidity, and hospital mortality. Results: Complete cytoreduction was possible in 80% of the patients. The median and the 5-year survival were 13 months and 32% respectively. No variable was found to be related to survival. Morbidity and hospital mortality were 30% and 0% respectively. The median follow-up time was 8.5 months and the recurrence rate 60%. Conclusions: Patients with rectal cancer and limited peritoneal dissemination are likely to be offered long-term survival if they undergo complete cytoreduction and perioperative intraperitoneal chemotherapy.

KEY WORDS: rectal cancer, peritoneal carcinomatosis, perioperative intraperitoneal chemotherapy, cytoreductive surgery, survival, morbidity, mortality

INTRODUCTION

Cytoreductive surgery in combination with perioperative intraperitoneal chemotherapy has been established as the most effective treatment strategy for colorectal cancer with peritoneal carcinomatosis.[1] The results of treatment in patients with rectal cancer and peritoneal carcinomatosis are conflicting. Some believe that these patients are offered the same survival benefit as those with colon cancer and peritoneal carcinomatosis.[2] Others report that there is no survival benefit even

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when complete cytoreduction is possible, because peritoneal carcinomatosis from rectal cancer is a particularly aggressive disease.[3]

The purpose of the study is to present the results of cytoreductive surgery in combination with perioperative intraperitoneal chemotherapy from one medical center.

PATIENTS AND METHODS

The present study is a retrospective one of a prospectively maintained database for patients who underwent surgery and perioperative intraperitoneal chemotherapy. From this database the records of the patients with colorectal cancer and peritoneal carcinomatosis that were treated from 2005 to 2014 were retrieved.

Data included age, gender, performance status, extent of prior surgery, extent of peritoneal carcinomatosis, completeness of cytoreduction, comorbidity, chemoperfusion agent, type of intraperitoneal chemotherapy (hyperthermic intraperitoneal-HIPEC, or early postoperative-EPIC), histopathological data, morbidity, mortality, recurrences, and survival. The performance status was assessed according to the Karnofsky performance scale. The extent of peritoneal carcinomatosis and of previous surgery was assessed according to peritoneal cancer index (PCI) and to prior surgical score (PSS) respectively. The completeness of cytoreduction was assessed according to the completeness of the cytoreduction score (CC-score).[4]

The past history of the patients was recorded in detail. All patients were assessed with physical examination, hematological-biochemical examinations, tumor markers, thoracic and abdominal CT-scanning, endoscopy, and, occasionally, whole body bone scanning.

All patients underwent surgery with the intent of complete cytoreduction. The types of peritonectomy procedures, the hospital mortality, the complications, the recurrences and the sites of recurrence were recorded. HIPEC and EPIC were performed using the same technique described elsewhere.[5] The proportion of patients with a given characteristic was compared with chi-square analysis or Pearson's test. Differences in the means of continuous measurement were tested with the Student's t-test. The survival curves were obtained with the Kaplan-Meier method. A two tailed p value of <0.05 was considered statistically significant.

RESULTS

The medical records of 74 patients with colorectal cancer and peritoneal carcinomatosis that underwent cytoreduction and perioperative intraperitoneal chemotherapy from 2005-2014 were retrieved. Ten of them (13.5%) were identified with rectal cancer. The general characteristics of the patients are listed in Table 1. The mean age of the patients was 56.7+12.8 (34-73) years. One patient had synchronous tumors of the sigmoid

Table 1. Patients' general characteristics

Variable	No of pts	%
Gender (M/F)	4/6	40/60
Performance status		
90-100%	7	70
70-80%	2	20
50-60%	1	10
PSS		
PSS-0	1	10
PSS-1	0	0
PSS-2	8	80
PSS-3	1	10
PCI		
PCI <10	7	70
PCI >10	3	30
CC-score		
CC-0	8	80
CC-1	1	10
CC-2	0	0
CC-3	1	10

and middle rectum and had not previously undergone surgery or any other treatment (PSS-0). The remaining patients had undergone surgery and had received systemic chemotherapy. Two of them had also received radiotherapy. All patients were in acceptable performance status. The extent of peritoneal carcinomatosis was limited (PCI <10) in the majority of the patients. Complete cytoreduction was possible in 8 patients (80%). The local disease was not resectable in one patient who underwent CC-3 surgery and did not receive intraperitoneal chemotherapy. Positive lymph nodes during initial surgery were found in 5 patients and at reoperation in 2 patients. Seven patients with CC-0 cytoreduction received HIPEC while one patient received EPIC. HIPEC and EPIC were administered in one patient who had undergone CC-1 surgery. Three patients that received HIPEC also received IV 5-FU and Leucovorine during surgery.

The performed peritonectomy procedures are listed in Table 2. There was no hospital mortality. The morbidity rate was 30%. The recorded complications were: wound infection in one patient, enterocutaneous fistula in one patient, and an intra-abdominal abscess in another. Neither mortality nor morbidity was found to be related to any one variable by univariate analysis. The mean hospital stay was 15 days (9-25).

Table 2. List of peritonectomy procedures

Procedures	No
Epigastric peritonectomy	7
Greater omentectomy	7
Right subdiaphragmatic	3
Splenectomy	1
Lesser omentectomy	1
Cholecystectomy	4
Right lateral peritonectomy	2
Left lateral peritonectomy	1
Pelvic peritonectomy	8
Sub-total colectomy	1
Right colectomy	1
Segmental intestinal resection	3
Abdominoperineal resection	1

The median follow-up time was 8.5 months. The median survival was 13 months and the 5-year survival rate 32% (Figure 1). With univariate analysis no variable was identified to be related to survival. During follow-up 6 patients (60%) were recorded with distant metastases. Currently there are 2 patients alive without disease, 3 patients died because of recurrence, and 5 patients are alive with disease. No variable was identified to be related to disease recurrence.

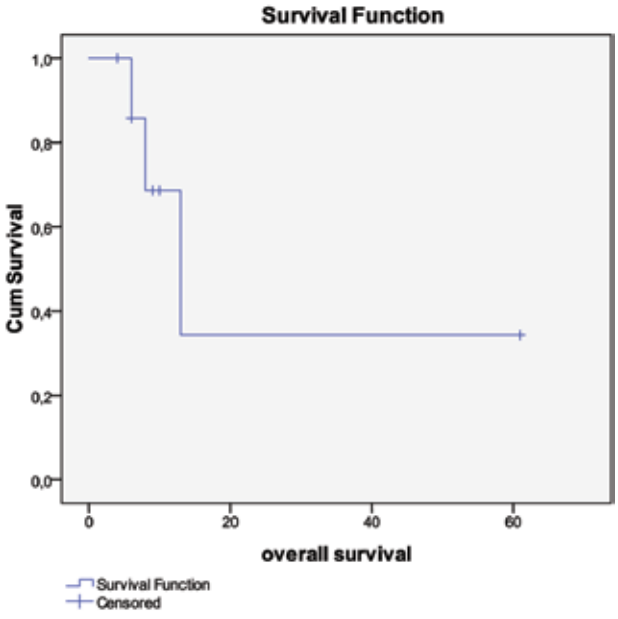

Figure 1. Overall survival in months in patients with rectal cancer and peritoneal carcinomatosis.

DISCUSSION

Cytoreductive surgery in combination with HIPEC has been established as the standard treatment for colorectal cancer with peritoneal carcinomatosis.[1,6,7] Two prospective randomized trials have shown that this treatment offers significant survival benefit compared to surgery and systemic chemotherapy.[6,7] The incidence of rectal cancer

with peritoneal carcinomatosis is low and varies from 4.4 to 23.3% of colorectal cancer with peritoneal carcinomatosis.[1-3,6-8] Peritoneal carcinomatosis from rectal cancer develops during surgery when the surgeon attempts to remove a tumor lying within narrow limits of resection such as the pelvis. Cancer emboli transected during surgical manipulations from interstitial tissue trauma, or severed lymphatic channels, or venous blood loss are entrapped in peritoneal surfaces. During wound healing, these emboli are deposited by fibrin. Inflammatory cells accumulate while growth factors operate and give rise to loco-regional recurrent tumors.[9] Spontaneous preoperative peritoneal carcinomatosis does not develop because the rectum is an extra-peritoneal organ. It seems that in one patient of the study with synchronous tumors of the sigmoid and rectum that had not previously undergone surgery, peritoneal carcinomatosis developed spontaneously because of the sigmoid tumor.

Peritoneal carcinomatosis from colon and rectal cancer is studied under the term colorectal cancer. Colon and rectal tumors are two distinct entities with different biological behavior. Limited survival of patients with rectal cancer and peritoneal carcinomatosis has been reported in one publication.[3] This finding has not been reproduced by other studies.[2,7,8,10,11] Despite the difference between colon and rectal tumors, it has been shown that the long term survival is the same and depends upon the completeness of cytoreduction, which is the most significant prognostic variable.[1-3,6-8,10,11] In our study the median survival of 13 months is consistent with the survival reported in other studies. The 5-year survival is 32% and one of the highest. The extent of peritoneal carcinomatosis is an equally significant variable of survival. The less the extent of the peritoneal dissemination the longer the survival.[1-3,5-8,11] The PCI is used for the selection of patients that may be candidates for complete, or near complete, cytoreduction. The majority of our patients had low PCI and complete cytoreduction was possible. Patients with high PCI are not usually candidates for surgery.[2,5-7,11] One of the most frequent sites of recurrence is the bed of the resected tumor. The recurrent tumor is unresectable if it infiltrates anatomical structures such as the iliac vessels or the sacrum, despite the extent of peritoneal carcinomatosis.[10] One patient in our study presented with an unresectable tumor adherent to the sacrum, despite the low PCI. The infiltration of the lymph nodes and the performance status has been identified as a negative prognostic indicator of survival in one publication but has not been reproduced by others.[2,10] The second cytoreduction, the use of systemic chemotherapy, and the ages under 65 years are other variables that have also been identified as prognostic indicators of survival in one retrospective study.[1] The number of patients with rectal cancer and peritoneal carcinomatosis is small in all these publications and definitive conclusions about long-term survival cannot be conducted. The morbidity rate varies from 23 to 63%. The mortality rate is between 0-4%.[1-3,5-8,10] Neither morbidity nor mortality is different from surgery for colon cancer with peritoneal carcinomatosis. In the present study, no variable was found to be of prognostic significance for survival, probably due to the small number of patients it included.

In conclusion, rectal cancer with peritoneal carcinomatosis appears to be similar to colon cancer with peritoneal carcinomatosis in regard to eligibility criteria, survival, morbidity and hospital mortality. Long-term survival is likely to be dependent on the ability of performing a complete cytoreduction in patients with limited extent of peritoneal carcinomatosis.

REFERENCES

1. Glehen O, Kwiatkofski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapyfor the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol 2004; 22: 3284-3292.
2. Elias D, Glehen O, Pocard M, et al. A compara-

tive study of complete cytoreductive surgery plus intraperitoneal chemotherapy to treat peritoneal dissemination from colon, rectum, small bowel, and nonpseudomyxoma appendix. Ann Surg 2010; 251: 896-901.
3. Gomes da Silva R, Cabanas J, Sugarbaker PH. Limited survival in the treatment of carcinomatosis from rectal cancer. Dis Colon Rectum 2005; 48: 2258-2263.
4. Sugarbaker PH. Management of peritoneal surface malignancy. The surgeon's role. Langenbeck's Arch Surg 1999; 364: 576-587.
5. Tentes AA, Korakianitis O, Pallas N, et al. Peritoneal colorectal carcinomatosis treated with cytoreductive surgery and perioperative intraperitoneal chemotherapy. Surg Science 2012; 3: 72-77.
6. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003; 21: 3737-3743.
7. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2008; 27: 681-685.
8. Kianmanesh R, Scaringi S, Sabate JM, et al. Iterative cytoreductive surgery associated withhyperthermic intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis of colorectal origin with or without liver metastases. Ann Surg 2007; 245: 597-603.
9. Sugarbaker P. Observations concerning cancer spread within the peritoneal cavity and concepts supporting an ordered pathophysiology. In: Peritoneal carcinomatosis: Principles and practice of management. PH Sugarbaker (ed), Kluwer Academic, Boston, Mass, USA, 1996, pages 79-100.
10. Votanopoulos KI, Swett K, Blackham AU, et al. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis from rectal cancer. Ann Surg Oncol 2013; 20: 1088-1092.
11. Rivard JD, Mc Connell YJ, Temple WJ, Mack LA. Cytoreduction and heated intraperitoneal chemotherapy for colorectal cancer: are we excluding patients who may benefit? J Surg Oncol 2014; 109: 104-109.

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