EUROPEAN JOURNAL OF ONCOLOGY
GIORNALE EUROPEO DI ONCOLOGIA

Official Organ of the Italian Society of Tumours
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Associato all'Unione Stampa Periodica Italiana

European Foundation of Oncology and Environmental Sciences "B. Ramazzini"
Fondazione Europea di Oncologia e Scienze Ambientali "B. Ramazzini"

Publisher
Mattioli 1885 - Spa
Casa Editrice

Autorizzazione del Tribunale di Parma n. 14/97 del 11/6/1997 - ISSN 1128-6598

The European Journal of Oncology is indexed by Excerpta Medica (EMBASE) and the Elsevier BioBASE
Il Giornale Europeo di Oncologia è recensito su Excerpta Medica (EMBASE) e su Elsevier BioBASE

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Editorial/Editoriale

Precautionary principle: scientific evidence and public health action

Il principio di precauzione: evidenze scientifiche e azioni di sanità pubblica

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Summary

The purpose of the present paper is to review conceptual and operational definitions of the precautionary principle (PP) connected with evaluation of scientific evidence and public health action. PP may be applied in cases in which risk is not well defined, but still there is some supporting evidence; it is an aspect of prudence that leads, in the case of uncertainty, to actions aimed at avoiding or limiting possible future harm. Many historical cases have shown the adverse effects of overlooking evidence of possible risk. This happened when interests other than public health were given priority, thus jeopardizing the ascertainment of causal links. After a long discussion on the meaning of PP and the limits to its application, there is today a wide consensus, also among international institutions such as the WHO, in adopting it as a generalized risk approach when risk assessment is not applicable. Several procedures, already well advanced at a theoretical level, have thus been proposed, and their application to practical cases should now be evaluated. Eur. J. Oncol., 11 (3), 153-156, 2006

Key words: **precautionary principle, scientific evidence, public health**

Riassunto

Scopo del contributo è la revisione delle definizioni concettuali e operative di principio di precauzione (PP) legate alla valutazione delle conoscenze scientifiche e alle azioni di sanità pubblica. Il PP si applica alle situazioni in cui il rischio non è ben definito, ma si hanno in merito delle evidenze parziali; è un aspetto della prudenza che induce, nell'incertezza, ad azioni volte ad evitare o a limitare possibili danni futuri. Molteplici sono i casi storici che hanno evidenziato le conseguenze di aver trascurato le evidenze su possibili rischi. Ciò è avvenuto quando sono stati tutelati primariamente interessi diversi da quelli della salute pubblica, ostacolando in vari modi la verifica dei nessi causali. Dopo un lungo periodo di discussione su significati e limiti di applicazione del PP, oggi c'è consenso a più livelli, anche da parte degli organismi internazionali come l'OMS, nel proporre il PP come un approccio generalizzato al rischio, da applicare quando non è possibile il *risk assessment*. Sono state proposte a tale scopo diverse procedure che, già maturate a livello teorico, vanno ora poste all'esame delle loro applicazioni a casi concreti. Eur. J. Oncol., 11 (3), 153-156, 2006

Parole chiave: **principio di precauzione, evidenze scientifiche, sanità pubblica**

The purpose of the present paper is to review the conceptual and operational definitions of the precautionary principle (PP), and to discuss the implications of its adoption in the domains of evaluation of scientific evidence and decision making.

In the original French approach, subsequently

Received/Pervenuto 14.4.2006 - Accepted/Accettato 22.5.2006
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endorsed by the European Union, the PP implies the adoption of a set of rules aimed at avoiding possible future harm, taking into account suspected, but not ascertained risks[1]. Measures should be proportional to the desired level of protection, non-discriminatory and consistent with measures adopted in areas where scientific data are available, based on a cost-benefit analysis (where feasible). Scientific research should be developed in order to reach a better knowledge and develop more appropriate strategies[2].

Precaution is an aspect of prudence[3], it mainly concerns those who have responsibilities in decision making, and it implies implementation of procedures including risk assessment, risk management and communication. Precaution thus stands in between the realm of prevention, that takes care of well-ascertained risks, and the realm of mere conjectures, where any hypothesis may be considered even in the absence of preliminary, incomplete evidence. Within this framework, the PP is not a moral principle *per se,* but rather an application of the ethical principle of non-maleficence, and it is based on the notions of awareness and responsibility[4] derived from the work of authors like Jonas[5] and Ricoeur[6]. Precaution in evaluating the long-term consequences of our actions is part of our overall moral responsibility. While civil responsibility has to do with the obligation to compensate harm, moral responsibility implies a commitment to avoid future harm, also in the presence of uncertainties in knowledge.

A complementary approach to precaution has been presented by Kriebel and Tickner[7], who refer to the notion of "anticipatory insight" (*Vorsorgeprinzip* of German authors). This approach is focussed on the issues of sustainability and innovation, it overcomes the need to demonstrate harm beyond any reasonable doubt and, rather, suggests choosing the best option after having compared different scenarios.

In both approaches, however, there is large agreement on the importance of anticipation, on the need to pay attention to the public's concerns and on the value of a risk management process that takes into account ethical issues besides technological and economical aspects.

In light of the aforementioned definitions of precaution, it may be shown that two aspects of public health activity are particularly involved by its application: evaluation of available evidence and decision making. Both these domains have been thoroughly explored by the European Environmental Agency in its well known report "Late lessons from early warnings"[8], based on the in-depth analysis of twelve significant case studies. In general, it can be seen that, following the report of a new suspected risk, an evaluation process starts and is developed in various institutional settings. Preventive action is suggested, but invariably a number of stakeholders deny the existence of causal links in order to delay their recognition, and thus postpone the adoption of remedial action[9,10]. This countering strategy may imply the discredit of positive studies, as happened when Monsanto experts unfairly criticized Hardell's and Axelson's epidemiologic studies on chlorophenoxyacid herbicides exposure and risk of soft tissue sarcoma, in their effort to influence the Royal Commission on the Use and Effects of Chemical Agents on Australian Personnel in Vietnam[11]. Notwithstanding these attempts to slow down the advancement of understanding, the Swedish studies were subsequently confirmed and contributed to the evaluation of 2,3,7,8 TCDD as a human carcinogen[12]. Other procedures employed to delay public health action include the creation of artificial controversies, such as those intended to downgrade the rôle of asbestos in the causation of mesothelioma by emphasizing the hypothesized aetiologic rôle of other factors like inheritance and viral infections[13-17]. A different kind of problem, finally, occurs when authoritative national or international committees recommend not to conduct a particular epidemiologic study. This was the case of a document by the International Commission for Non-Ionizing Radiation Protection (ICNIRP)[18] that recommended not to encourage further studies on electromagnetic fields and reproductive health. The subsequent publication of two high quality studies on spontaneous abortion and 60 Hz magnetic field[19,20] showed significantly increased risks of spontaneous abortion associated with residence in dwellings with exposure levels of 1-5 μT and the aforementioned ICNIRP statement appeared to be totally unjustified.

The latter example may be helpful in introducing the debate on the application of the PP to electromagnetic fields exposure. In an early stage of the discussion, some authors suggested a relatively low-profile use of the PP in this domain, for example as a means to favour public acceptance of new emitters[21], or as a general approach, leaving decision making to be guided by cost-benefit analysis alone. Within this framework it seems interesting to mention the approach adopted by the Italian League for the Fight against Cancer[22] that recently defined the appropriate domain for precautionary approach after a thorough review of existing epidemiologic and experimental studies on 50-60 Hz magnetic fields: *"It seems reasonable to concentrate preventive action inspired by precaution on subjects with highest exposure levels, namely those above 0.5 μT"*. This conclusion is specific, pragmatic, and open to be modified whenever new knowledge becomes available.

The increasing relevance of the PP in environmental and in public health sciences was enlighted by many

contributions in the publication of the European Ramazzini Foundation "The precautionary principle. Implications for research and prevention in environmental and occupational health"[23]. The contribution underlines many aspects of precaution: ethical, methodological and practical questions are explored and proposals for applications are developed in the final draft statement by the Collegium Ramazzini Council of Fellows. In the last two years some authors have provided new contributions to the discussion on precaution in public health. Among them Grandjean[24], after a detailed review of the definitions of the PP, emphasized the need to develop frameworks for an "unambiguous" application of the PP, that requires explication of the legal and cultural circumstances in which the evaluation and decision making process take place. Two points in this frame deserve a special mention: the notion that lack of information (deriving from lack of scientific research) currently offers "automatic" rewards to industry, or in general to the producer of a given agent or technology, and the awareness that open and transparent procedures are needed in order to avoid biased decisions with regard to assessing causal links. On this ground, Grandjean develops the concept of a precautionary research paradigm, that implies a shift in scientific research from the repetition of previous studies aimed at reducing already limited uncertainty, towards search for early indicators of emerging environmental health issues, interest for vulnerable groups and subjects, priority for topics related to ecosystem integrity and care for future generations, as well as accountability for all implicit options of study design and conduction. This approach has been endorsed by the Collegium Ramazzini, and has become the foundation of a recent position paper[25].

Recently, WHO has been developing a practical framework to assist its members in the development of their public health policies guided by the application of the PP in areas where science is not yet adequate for rigorous risk assessment. The basic premise of the WHO framework is that precaution should be applied to all aspects of managing an actual or potential risk. The framework has precaution as an overarching philosophy, from evaluating risk and generating options to dealing with uncertain risks, to implementing actions to reduce possible health risks and monitoring the effectiveness of the actions taken[26].

A general frame for the application of precaution, finally, has been presented by WHO-Europe in the 2004 Budapest Conference of the Ministries of Environment and Health of the European Region[27]. This approach is intended to improve tools for analysis of complex systems, in order to gain new insight into the health implications of ecosystem impairment, to increase transparency in decision making, to support research and to train public health officers in early detection of new risks. It is well known, and perfectly understandable, that public health officers have traditionally privileged preventive action aimed at contrasting well ascertained risks. It can be shown, though, that precaution is not antithetic to prevention, but in some instances it may also provide effective tools for tackling ascertained preventable risk factors. Precaution, furthermore, can contribute to defining priorities in the adoption of remedial action, especially if it incorporates an idea of favouring worse-off situations, as it is suggested by the adoption of a maximin approach[28]. The implementation of precaution thus appears to hold on three main notions[29]. First of all, a proactive approach is needed, thus revaluating the concept of anticipatory insight that was previously introduced by Kriebel and Tickner[7], in order to avoid the risk of being reactive if the discussion is merely concentrated on the minimum amount of evidence needed to take action. Secondly, the production of new knowledge requires innovative, multidisciplinary studies, mainly focussed on "upstream" causes of disease, characterized by transparency, accountability and participation. The third step will thus be a precautionary evaluation based on the comparison of the environmental and health impacts of different alternative options. This will require specification of the appropriate precaution level according to the problem being studied, the determination of technical, informative and practical interventions, and the design of evaluation procedures for the detection of undesired effects.

In conclusion, any use, criticism or comment on the adoption of the PP should be qualified by a clear understanding of the fundamentals of precaution. This awareness should inspire the development of precautionary action in response to specific problems and as a function of priority setting, and the use of a case-study approach, not only in a theoretical way but also and mainly in real cases and at different levels (communities, populations, states) in order to compare and evaluate adopted and recommended procedures.

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Eur. J. Oncol., vol. 11, n. 3, pp. 157-163, 2006

Toxic and carcinogenic chemical exposure: medical monitoring for early detection of latent disease

Esposizione a composti chimici tossici e cancerogeni: monitoraggio medico per la diagnosi precoce delle malattie latenti

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Summary

Medical monitoring is the design and application of a set of medical histories, examinations, tests, and/or procedures for the purpose of detecting specific, previously unrecognized and future latent diseases, injuries, and other medical conditions. Medical monitoring is generally focussed on individuals who are at increased risk of specific diseases, injuries, and other medical conditions for one or more reasons, such as occupational or environmental exposure to carcinogenic chemicals. Medical monitoring is performed under various contexts, not limited to the following: medical monitoring, mandated by the Occupational Safety and Health Administration, of workers who are at increased risk of specific diseases because of workplace exposures to specific hazardous chemicals; medical monitoring, undertaken by a governmental public health agency, of community residents who lived near landfills with toxic and carcinogenic chemicals; and medical monitoring of individuals who are awarded future medical monitoring via legal court proceedings. Medical monitoring has been established as a legal remedy in some states, doctrine of which is discussed in this manuscript. Medical professionals are asked to address and apply specific issues of medical monitoring in legal cases. The court cases described here help with guiding the medical professional in the forensic application of medicine to law.

Riassunto

Il monitoraggio medico consiste nella programmazione ed applicazione di una serie di anamnesi, esami, test e/o procedure mediche al fine di individuare malattie, danni ed altre situazioni di interesse medico latenti, precedentemente non riconosciuti, che si sarebbero manifestati in futuro. Il monitoraggio medico è di solito rivolto a soggetti che sono ad aumentato rischio di particolari malattie, danni ed altre situazioni di interesse medico per una o più ragioni, come l'esposizione professionale o ambientale a composti chimici cancerogeni. Il monitoraggio medico viene eseguito in vari contesti, che non si limitano ai seguenti: monitoraggio medico, richiesto dall'*Occupational Safety and Health Administration*, dei lavoratori ad aumentato rischio di malattie specifiche dovute ad esposizioni lavorative a particolari composti chimici pericolosi; monitoraggio medico, avviato da agenzie governative di sanità pubblica, di popolazioni residenti presso discariche di composti chimici tossici e cancerogeni; e monitoraggio medico di individui ai quali viene concesso per il futuro mediante procedimenti legali. Il monitoraggio medico è stato stabilito in alcuni Stati degli Stati Uniti d'America come risarcimento legale, le cui basi dottrinali vengono discusse in questo lavoro. Ai medici viene richiesto di individuare ed applicare particolari elementi di monitoraggio medico in casi di interesse legale. I casi discussi qui aiutano a guidare i medici

Received/Pervenuto 3.4.2006 - Accepted/Accettato 15.5.2006
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Examples of future medical monitoring in populations exposed to carcinogenic agents are discussed. Based on the medical literature and legal doctrines, we recommend future monitoring programmes for populations exposed to carcinogenic chemicals whose cancer risks are increased substantially. Eur. J. Oncol., 11 (3), 157-163, 2006

Key words: **future medical monitoring, guideline, latent disease, legal cases, liver cancer, lung cancer, screening**

nell'applicazione forense della medicina alla legge. Vengono discussi esempi di monitoraggio medico futuro nelle popolazioni esposte ad agenti cancerogeni. Sulla base della letteratura medica e delle dottrine legali, raccomandiamo programmi di monitoraggio futuri per le popolazioni esposte a composti chimici cancerogeni, i cui rischi di cancro sono decisamente aumentati. Eur. J. Oncol., 11 (3), 157-163, 2006

Parole chiave: **monitoraggio medico futuro, linee guida, malattie latenti, casi legali, cancro epatico, cancro polmonare,** ***screening***

Introduction

Medical monitoring is an accepted, medico-legal concept throughout several states in the United States. Awards for medical monitoring of latent disease historically originated from individuals exposed to asbestos. The concept has been applied to exposures to other toxic chemicals that increase the risk of latent diseases, such as cancer.

The Agency for Toxic Substances and Disease Registry (ATSDR) has established criteria for determining the appropriateness of a medical monitoring programme under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). The outcome criteria, as published by the ATSDR, are as followed: 1) there should be documented human health research that demonstrates scientific basis for reasonable association between a specific adverse health effect (such as an illness or change in biological marker of effect); 2) previous studies of human populations must demonstrate a reasonable association between a particular exposure and an adverse health effect: in order to make that inference, consideration should be given to the strength, specificity, and consistency of the association among the identified studies; 3) the period of exposure (including the timing and duration of exposure) in its relationship to the latency period for the disease or illnesses should also be examined if information is available; and 4) consideration should be given to whether the association has demonstrated a dose-response relationship and whether the association is consistent with the existing body of knowledge[1]. The criteria may be applied broadly to occupational, epidemiological, and environmental studies involving affected individuals and populations.

The ATSDR further states that monitoring should be directed at *"detecting adverse health effects that are consistent with the existing body of knowledge and amenable to prevention and/or intervention measures"*[1]. Adverse health effects pertain to those described *"in the literature as caused by the agent"*, or *"by similar agents taken into account by structure and activity relations"*[1]. An easily detectable effect is one that can be found on clinical examination or through the use of simple diagnostic tests in an outpatient setting. Also, test procedures must be acceptable to the patient and the community (emphasis clearly on informed discussions with the patients). Diagnostic tests must be non-experimental, relatively non-invasive, and easy to administer. In addition, early detection of adverse health effects should allow for treatment and intervention that interrupts the progress of the disease, improves upon the prognosis of the disease, improves the quality of life of the individual, and/or be amenable to primary prevention. If the adverse health effects of concern are neither easily detectable nor medically treatable, then medical monitoring would not be beneficial and would not be an appropriate public health activity nor a legal remedy for those exposed to toxic agents with latent disease.

The American Cancer Society (ACS) Guidelines for Early Detection of Cancer 2005[2], address medical monitoring for the general population. The ACS Guidelines do not specifically address occupational and/or environmental, carcinogenic exposures.

The United States Preventive Services Task Force (USPSTF) provide clinical categories to assess the merits of preventive measures, including screening tests for cancers[3]. However, the USPSTF also do not address occupational and/or environmental, carcinogenic exposures.

Screening programmes for populations with risk of latent disease should consist of the following attributes: 1) the cancer will be a major health problem; 2) the cancer will be more treatable if detected early; 3) tests should be acceptable to those eligible; 4) the test should

be inexpensive; 5) the test should have high sensitivity; 6) the test should have high specificity; 7) screening will have been shown to reduce mortality under randomized controlled trials; and 8) screening will have been shown to be a cost-effective means of controlling the specific cancer[4]. Furthermore, eligibility is for those individuals who have reasonable probability that they will benefit from being screened. Screening tests should be repeated at intervals determined by the natural history of the cancer, and represent a judgement with regards to the benefits of more frequent screening.

Guidance from court decisions

The following court decisions represent the concept and application of future medical monitoring. Louisiana legislature has mandated medical monitoring as a compensable event to a party exposed to toxic chemicals with a potential for latent disease, such as cancer[5]. In the case of Friends for All Children *vs* Lockheed Aircraft Corporation, the United States Circuit Court of Appeals for the District of Columbia allowed plaintiffs to recover costs for future medical monitoring in the absence of an injury or present physical disease[6]. The Circuit Court found that the award of future medical monitoring was in the nature of an equitable remedy, i.e., a remedy of fairness in order to avoid greater damages in the future. The court also determined that the need for medical monitoring was medically warranted and reasonable since it would serve to prevent far more serious harm in some of these cases.

The case of Ayers *vs* Township of Jackson is an example of medical monitoring without an existent physical injury or manifestation of disease[7]. According to the court, elements that justified medical monitoring recovery were: 1) significant exposure of the individual; 2) exposure to a proven hazardous or toxic substance; 3) significant, increased risk of contracting serious disease as a result of exposure; 4) increased risk making the need for periodic examination reasonably necessary; and 5) monitoring and testing procedures extant, the benefits derived from which exceed the social and economic costs.

In the case of Michael Buckley *vs* Metro North Commuter Railroad Co., future medical monitoring was granted for asbestos exposure despite the fact that quantitative levels of exposure were not available[8]. Testimonies of the experts described workers exposed substantially to asbestos as *"appearing as snowmen"*. Evidence of exposure while lacking in a definitive threshold dose, *"was graphic in meeting the necessary notions"* of the court as to the "level of proof required".

In Gerardi *et al*. *vs* Nuclear Utility Services, Inc., the court stated a defendant is liable for medical monitoring expenses incurred by plaintiff due to invasion of the body by toxic substances through negligent exposure[9]. As such, the standard of monitoring expenses is lowered to a certain extent. The court of Buckley specified the term when medical monitoring costs are applicable to toxic exposures. The court agreed with the Third Circuit, *"that the plaintiff: prove that by reason of the exposure to the toxic substance caused by the defendant's negligence, a reasonable physician would prescribe for her or him a monitoring regime different than the one that would have been prescribed in the absence of that particular exposure"*[8]. The key notion here is that a reasonable physician prescribing tests for medical monitoring would have otherwise not absent that particular exposure. The indication is that exposure to the toxic substance causes incremental risk of harm. Therefore, the court recommended, *"a plaintiff may recover only if the defendant's wrongful acts increased the plaintiff's incremental risk of incurring the harm produced by the toxic substance enough to warrant a change in the medical monitoring that otherwise would be prescribed for that plaintiff"*[8]. Whereas the carcinogenicity of certain, toxic chemicals are established by epidemiological studies, the Litmus test for prescribing medical monitoring is not that of epidemiological peer-reviewed literature (so that the medical doctor clearly understands, medical causation is not necessarily equal to or does not necessarily mean treatment, i.e., medical monitoring). The Litmus test for medical monitoring is twofold: 1) an established increased risk of latent disease; and 2) the recommendation of a reasonable physician to prescribe monitoring.

An important consideration for medical monitoring is described in asbestos exposure and early detection of lung cancer. The purpose is not just to intervene early and thereby reduce the chance of premature death, rather to assist in identifying and separating those individuals most likely to develop the disease from those who will not[10].

In the case of Tom Hansen *et al*. *vs* Mountain Fuel Supply Company *et al*, the court doctrine indicated that proof of exposure requires exposure to toxic substance caused by negligence of another party, which increases the risk of serious disease, injury or illness, and for which medical surveillance is available for early detection[11]. The case demonstrates the principle of medical monitoring and establishes that early detection, followed by treatment, will benefit the individual.

In the case of Harry F Gibbs Sr. *et al*. *vs* E. I. DuPont de Nemours & Co., Inc. *et al*., the State of New York

allowed plaintiffs to recover medical monitoring upon sufficient proof of exposure[12]. The state court allowed plaintiffs medical monitoring claims for asbestos exposure from handling fine fibre content of asbestos gaskets.

The United States Court of Appeals for the Third Circuit, in a Federal Employer's Liability ACT (FELA) claim, reached the opinion that a plaintiff must prove, due to his exposure to toxic substance caused by defendant's negligence, that a reasonable physician would prescribe a monitoring regimen different from one that would be required in the absence of the exposure[13, 14]. Under the criteria established by Third Circuit Court, the actual levels or risk assessment are not demanded as the threshold requirement.

The decision of Lowell V. Burns *et al*. *vs* Jaquays Mining Corporation, D.W. *et al*. crystalizes the opinions expressed by previous courts and helps guide the medical professional in medical monitoring cases[15]. Specifically, the court cites the decision of Ayers *et al*. *vs* Township of Jackson[7] and agrees *"that when the evidence shows through reliable expert testimony predicated on the significance and extent of exposure… the toxicity of [the contaminant], the seriousness of the diseases for which the individuals are at risk, the relative increase in the chance of onset of the disease in those exposed and the value of early diagnosis,… surveillance to monitoring the effects of exposure to toxic chemicals is reasonable and necessary"*[15]. The Burns Court added: *"Compensation for reasonable and necessary medical expenses is consistent with well accepted legal principles. It is also consistent with the important public health interest in fostering access to medical testing for individuals whose exposure to toxic chemicals creates an enhanced risk of disease. The value of early diagnosis and treatment for cancer patients is well documented"*[15]. A common posture by those who oppose medical monitoring is the argument that physicians should prove a disease is likely in the event of toxic exposures. The Burns Court actually clarifies this issue: *"It is inequitable for any individual, wrongfully exposed to dangerous toxic chemicals but unable to probe that disease is likely, to have to pay his own expenses when medical intervention is clearly reasonable and necessary"*[15]. The court's decision adds credence to the Litmus test for medical monitoring, of medical reason and necessity, as opposed to the need of peer-reviewed, epidemiological studies to be proven. This statement is also medically sound, because for many toxic and dangerous chemicals, epidemiological studies are not always feasible or available.

Following the guidelines of reasonable medical community and the spirit of relevant court decisions, we describe two target organ cancers where early detection tools are available, predictive, cost-effective, and lead to cure or substantial increase in life expectancy (not all organ systems are covered in this manuscript, i.e. renal, gastrointestinal, haematological systems, etc.).

Examples of recent advanced technology in medical monitoring for early detection: liver cancer and lung cancer

The following describes two classes of cancers, where the existing body of knowledge describes sensitive and effective methods for early detection of latent disease.

Liver cancer

The incidence of hepatocellular cancer (HCC) is on the rise. In a peer-reviewed paper, Everson[16] examines the issues of identifying subgroups of patients at high risk for HCC, with consideration for liver transplantation. The author states that timely performance of liver transplantation is curative in patients with early stage HCC. A cost analysis supports the screening and identification of high-risk individuals. The medical costs of screening and treatment is $285,294.00 per cured case. If the cure is assumed to be associated with 75-85% chance for high-quality 10-year survival, Everson estimates the cost to be $35,000.00 to $40,000.00 per quality-adjusted life-year. This cost-benefit analysis compares favourably with published rates for breast cancer screening[16]. In addition, technology continues to improve and aid in early detection of HCC. Magnetic resonance imaging (MRI) studies of liver lesions less than 20 mm have found MRI to be a useful diagnostic tool in determining early liver cancers[17].

With regards to screening, Collier and Sherman[18] state *"[the] disease must be common and must have a substantial morbidity and mortality*". HCC is the fourth most common cancer in the world. Age-standardized incidence varies from 3 per 100,000 in North America to 80 per 100,000 in China. When risk calculation has increased substantially from 3 per 100,000 (baseline) as a result of exposure to liver carcinogens, the concept that the disease must be common and have substantial morbidity and mortality has been fulfilled to require MRI liver images for early detection of liver cancer. An easily identifiable target population includes individuals with chronic hepatitis B and C, individuals exposed to liver carcinogens, and individuals with major risk factors of increasing HCC. In other words, there exist no "epidemiological studies" in large-scale populations with regards to HCC and liver carcinogens, such as vinyl chloride.

Long-term experimental animal studies by Maltoni *et al*[19] have demonstrated that vinyl chloride is a multi-potent carcinogen affecting various organ tissues, among those the liver. Scientific peer-reviewed literature describes vinyl chloride as a known human carcinogen to the liver, and therefore a target population is identifiable, i.e., a population exposed to vinyl chloride at sufficient levels to increase the risk from background (3 in 100,000) to substantially more, or as described by the Third Circuit FELA case, where a reasonable physician would prescribe a monitoring regimen different from one that would be required in the absence of the exposure[13, 14].

Collier and Sherman[18] indicate that screening tests must have low morbidity, high sensitivity, and high specificity. Indeed, the parameters of HCC screening are fulfilled by using screening tests for alpha-foetoprotein, which is only a surveillance screening study, in conjunction with ultrasonography of the liver, which has 71-78% sensitivity and 93% specificity. The combined positive predictive value would be 73% for a reported surveillance interval from 3 to 12 months.

In screening for HCC, Collier and Sherman[18] call for standardized recall policies. Indeed, among recall policies are MRI studies, which detect smaller tumours with 81% sensitivity for tumours less than 2 cm. Sensitivity can be improved further by using techniques such as lipiodol computed tomography (CT), which has a sensitivity of between 93-97%. The authors also contend that effective therapy must exist. For HCC, possible therapy includes hepatic resection and liver transplantation.

Surveillance should reduce the mortality of the disease. Collier and Sherman[18] indicate that tumours detected by surveillance, 50-75% unifocal and 3 cm or less in size, are potentially curable. The authors recognize recently reported high 3-year survival rate for liver transplantation for small tumours, which in today's medical practice increases use of this form of therapy and increases life expectancy.

Collier and Sherman[18] also state that the ideal manner to determine the efficacy of a surveillance programme for hepatic carcinoma would be to conduct a randomized, control trial of surveillance *versus* usual care with disease-specific and all-cause mortality as endpoints. The sample size required depends on the incidence of hepatic carcinoma. Assuming an incidence rate of 0.4-0.5%, sufficient sample size may require up to 12,000 subjects. Unfortunately, this may not be feasible in North America. A suggested alternative is to compare surveillance with alpha-foetoprotein alone to ultrasound alone, and alpha-foetoprotein and ultrasound combined. However, such a study would not establish the efficacy of surveillance. Therefore for a specific high-risk group, there needs to be a reliance on current, medical data available in the peer-reviewed scientific literature.

Screening without evidence of efficacy is unethical, because surveillance involves not only the inconvenience of regular blood tests, ultrasounds, and extensive secondary radiological imaging, but also results in the diagnosis, albeit early, of tumours that are still untreatable[18]. However, if only small hepatic cancers are amenable to treatment, then the approach may be to use the best surveillance tools to find small hepatic cancers and to study the optimal treatment of these lesions through randomized, controlled therapy trials. Given the low resectability rates and survival after surveillance in most western centres, this is the only way that continued surveillance can be justified. In other words, if treatment trials are not available in a given area for patients with small hepatic carcinomas, surveillance is inappropriate (at least in North America). Thus, Collier and Sherman[18] discuss hepatitis C, hepatitis B virus and liver cirrhosis, and do not address specifically the HCC caused by exposure to vinyl chloride. At present, epidemiological studies on other liver carcinogens (other than hepatitis C) are lacking, and are unlikely to be accomplished at any time soon. Therefore, the rationale would be to provide future medical monitoring and surveillance for early detection after discussion of the patients with their primary treating physicians. Of course, any study and treatment modality are subject to informed consent and discussion between patient and their primary treating physicians. If remedy is given to the exposed individual and the individual decides to decline, it is within their rights to do so. Nevertheless, since a sensitive and effective method to detect early, small HCC is reasonably priced and a cure (relative to non-cure) is beneficial, it is our position that patients exposed to known, human carcinogens of the liver and who are at substantial risk should qualify for medical monitoring.

Lung cancer

Low-dose, spiral CT has been utilized in the early detection of lung cancer. Sone *et al*[20] were able to detect eleven times the expected annual numbers of lung cancer with low-dose, spiral CT (55% sensitivity and 95% specificity of detecting surgically-confirmed lung cancer). Bechtel *et al*[21] evaluated lung cancer detection using CT thoracic scans. The authors concluded that through identifying patients (high-risk) exposed to carcinogens in the lungs by questionnaires and CT scans in combination with cytology, they were able to find a higher number of early lung cancers at a reasonable cost of $11,925 per patient.

Gohagan *et al*[22] demonstrated with spiral CT scanning of the lung convincing data of feasibility to detect early

lung cancers. Early detection directly leads to increased survival. Henschke[23] was able to demonstrate an estimated five-year survival rate of 60-80% compared previously to 15% with low-resolution CT scan. Furthermore, Wisnivesky *et al*[24] showed that with decrease in size of lung cancer on early detection, life expectancy increases. Survival rates were statistically significant for 5-15 mm tumours at 69% (95% confidence interval: 64-74%). This is a major advancement for early detection. Not long ago, once a patient was diagnosed with lung cancer, life expectancy was short and grim. Brant-Zawadzki[25] states that *"it seems silly to consider that some of us readily accept a woman's right to choose an abortion but not her right to choose screening CT, despite the fact that more women die of lung cancer than breast cancer"*. Low-dose spiral CT screening is a sensitive technique for early-stage lung cancer[26].

Critics are concerned with a 15% false-positive rate for lung spiral CT. However, technological advances improve upon false-positives. Bastarrika *et al*[27] have shown that follow-up with F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) of the false-positive nodules essentially eliminates the problem. The authors conclude that early detection of lung cancer after a carefully designed, low-dose spiral CT is possible, and that this strategy may improve chances for cure.

Spiral lung CT is sensitive, predictably valuable, able to early detect lung cancer, and prolongs life. Five years ago, when the medical community relied on chest X rays and sputum cytology, late-stage diagnosis of lung cancer was analogous to a "death sentence". If we can reach a 5-year survival rate of 60-70% after early detection with today's advanced technology, it will be immoral medically and perhaps breach the standard of care to deny such a treatment modality to specific patients exposed to toxic-carcinogenic chemicals to the lung. Public health policies do not recommend spiral CT of the lung to the population at-large. However, our study discusses the applicability of advanced medical technology for future medical monitoring in individuals exposed to carcinogenic chemicals with increased risk of latent disease, where individuals otherwise would not be in need of medical monitoring. The aim of this study is not to address public policy or concerns with regards to cigarette smoking, but rather address specific populations exposed to carcinogenic chemicals.

Discussion

Technology deemed effective in early detection, cure, and/or extending life expectancy of individuals exposed to carcinogenic agents and who have an increased risk of a latent disease is available. Thus, in our opinion it is immoral not to offer such a remedy to these individuals. The legal concept of future medical monitoring for such cases ties in with the advancement in medical biotechnology. In order to undertake a medical monitoring programme, the following guidelines have been considered and found compelling:

- the individuals to be monitored should be at increased risk of a specific latent disease, injury, or other medical condition as a result of the specific carcinogenic exposure;
- there should be methods, such as medical histories, examinations, tests, and/or procedures, available that can detect this specific disease, injury, or other medical condition at a latent stage;
- these methods should not represent undue risk to those being monitored;
- the necessary follow-up examinations, tests, and procedures to make a conclusive diagnosis, as well as health care services for the medical management of the disease, injury, or other medical condition should be available and accessible;
- these methods should enable those being monitored to have a better quality and/or longer length of life after diagnosis of a previously unrecognized disease, injury, or other medical condition than they otherwise would have had if there were no medical monitoring programme;
- there should be a system established and maintained to review the findings of the medical monitoring programme.

Conclusion

The medical professional should rely on the synthesis of public health policy and guidance from court decisions described above to benefit patients and the public. Workers or residents who have been exposed to toxic carcinogenic agents and stand to experience a substantial increased risk of developing latent disease (cancer) should undergo future medical monitoring after demonstrating that: 1) exposure was substantial and considerably increases the risk of developing latent disease, or alternatively a reasonable physician would have prescribed the studies under these conditions; 2) medical monitoring for the specific condition is effective, has been studied, and is shown to be specific; 3) monitoring is cost-effective; 4) individuals are given informed consent; and 5) medical monitoring would have otherwise not been required and/or available to the exposed party.

Acknowledgements

The authors thank Jill Tremblay for her efforts in transcribing this manuscript.

Disclosure

Nachman Brautbar, M.D. serves from time to time as an expert in litigation related to toxic exposures. This manuscript was not authored for litigation purposes. No funding for this manuscript was provided by chemical industry, attorneys or public organizations of any form or shape. The opinions expressed in this manuscript do not necessarily reflect that of any organizations the authors are affiliated with.

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Eur. J. Oncol., vol. 11, n. 3, pp. 165-176, 2006

Comparison of two models of cancer risk estimation: a statistical analysis

Confronto di due modelli per la determinazione del rischio di cancro: analisi statistica

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Summary

The experimental mortality data from research conducted at the Argonne National Laboratory on the effects of exposure of $B6CF_1$ mice to whole-body irradiation, gamma rays (0 cGy to 1839 cGy) or fission neutrons (0 cGy to 226 cGy), were analyzed to assess the shape of the dose response and the effects of fractionation with respect to cancer mortality. The mice were grouped based on their sex, exposure pattern (single exposure or 60 once-weekly exposures) and total accumulated dose of exposure. The Cox proportional hazards model was used as an empirical model, while the two-stage clonal expansion model was used as the biologically-based cancer model in which information on the carcinogenesis process is incorporated into the model. Both the neutron and gamma dose response curves appear linear at the lower doses (less than 30-40 cGy), before the non-linearities become evident. The findings suggest a reduction in the effectiveness of gamma irradiation with fractionation (dose rate effectiveness factor = DREF ranged from 1.2-1.5) for solid tumours, while the effectiveness of neutrons increases with fractionation (DREF = 0.7). For lymphoreticular tumours the DREF values were 3.7-5.8 and 0.2-0.3 for gamma and neutron, respectively. For acute exposures the estimated relative biological effectiveness (RBE) for neutron was 1.4 and 24 for lymphoreticular and solid tumours, respectively.

Riassunto

I dati sperimentali di mortalità ottenuti dalla ricerca condotta dal Laboratorio Nazionale di Argonne, negli Stati Uniti, sugli effetti dell'esposizione di topi $B6CF_1$ a irradiazioni sull'intero corpo, a raggi gamma (da 0 cGy a 1839 cGy) o a neutroni da fissione (da 0 cGy a 226 cGy), sono stati analizzati per valutare la funzione dose-risposta e gli effetti del frazionamento sulla mortalità per cancro. I topi sono stati suddivisi in base al sesso, al tipo di esposizione (esposizione singola o 60 esposizioni una volta alla settimana) e alla dose totale di esposizione accumulata. Il modello a rischi proporzionali di Cox è stato utilizzato come modello empirico, mentre il modello di espansione clonale a due stadi è stato utilizzato come modello di cancro su base biologica, in cui le informazioni sul processo di cancerogenesi vengono incorporate nel modello stesso. Sia la curva dose-risposta dei neutroni che quella dei raggi gamma appaiono lineari alle bassi dosi (meno di 30-40 cGy), prima che le non-linearità delle curve diventino evidenti. Questi risultati suggeriscono una riduzione dell'efficacia dell'irradiazione gamma con il frazionamento (il fattore di efficacia per il tasso di dose = *dose rate effectiveness factor* = DREF ha valori da 1,2 a 1,5) per i tumori solidi, mentre l'efficacia dell'irradiazione a neutroni aumenta con il frazionamento (DREF=0,7). Per le neoplasie linforeticolari i valori del DREF erano 3,7-5,8 per i raggi gamma e 0,2-0,3 per i neutroni,

Received/Pervenuto 9.6.2006 - Accepted/Accettato 6.7.2006
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Both models suggest that a linear dose-response curve provides an adequate fit to the data. Eur. J. Oncol., 11 (3), 165-176, 2006

Key words: **cancer, gamma rays, neutrons, mouse**

rispettivamente. Nelle esposizioni acute l'efficacia biologica relativa (*relative biological effectiveness* = RBE) stimata per i neutroni era 1,4 per le neoplasie linforeticolari e 24 per i tumori solidi, rispettivamente. Entrambi i modelli suggeriscono che una curva dose-risposta lineare rispecchia adeguatamente i dati. Eur. J. Oncol., 11 (3), 165-176, 2006

Parole chiave: **cancro, raggi gamma, neutroni, topo**

Introduction

Many late effects from exposure to ionizing radiation, including cancers, have been described in the literature. The identification and quantification of radiation-induced health effects is an important and complex issue. The recommendations for radiation safety and protection from the International Commission on Radiological Protection (ICRP) are made based on the risk estimates for late effects from low dose radiation[1]. A major obstacle in this process is the limited availability of data to directly measure the health effects of radiation on human populations. The problem is further hampered because the data on human exposures do not include the energy spectrum and patterns of exposure that are most relevant. One way to circumvent this problem is to use experimental data from laboratory animals and extrapolate across species to man[2].

Another issue to consider is that there are many models available to generate risk estimates. Some models are empirical, purely mathematical and driven by the data, while others are mechanistic and attempt to incorporate biological plausibility within the mathematics. Both categories of models have a history in radiation biology and different issues that related to them. The Cox proportional hazards model is an empirical model that uses time to event as well as covariate data to describe the data, without considering what is happening biologically. A parametric form of the covariate effect is assumed, while the baseline hazard rate is treated non-parametrically, allowing inferences to be made about the covariate effect, but not the baseline hazard. The two-stage clonal expansion model, also referred to as the Moolgavkar-Venzon-Knudson model (MVK model), is a biologically-based cancer model that accounts for clonal expansion, replication, differentiation, and mutation of the cells in the first altered state (initiated cells) as well as the mutation rates of normal cells. Questions as to whether or not non-linearities exist at low doses in the dose-response curve add to the issue and debate over which model should be used when investigating low dose effects[3].

The two-stage clonal expansion model has been applied to data on radiation-induced cancers in humans and rats as well as other environmental cancers. The A-bomb survivors data indicated an initiation effect, but contained no information on promotion[4]. In studies of Colorado uranium miners exposed to radon[5] and radon-exposed rats[6] a promotion effect was necessary to describe the data.

The two-stage clonal expansion model assumes that at any given time there are a large constant number of somatic cells susceptible to genetic transformation (X_0); since all of the animals in this data were irradiated as young adults, the number of normal cells is constant through the observation. Initiated cells, resulting from a somatic mutation ($X_1(t)$) reproduce in a stochastic manner, and once a malignant cell ($X_2(t)$) is formed by a second mutation, it will inevitably become an observable tumour[7,8].

The model consists of four time-independent parameters μ_1, β, δ, and μ_2 described in fig.1. Each normal cell has a non-zero probability of undergoing a transformation into an initiated cell, at a rate of ν per unit time per cell, so that $\mu_1 (= \nu X_0)$ is a constant transition rate per unit time. Each initiated cell may undergo three events: they can replicate into two intermediate cells at a rate β per unit time per cell, die at a rate of δ per unit time per cell, or divide into one malignant cell and one initiated cell at a rate of μ_2 per unit time per cell.

There is a lack of identifiability because not all four of these parameters can be determined from tumour incidence data[9], therefore, it is only possible to calculate three unique estimates for the parameters. In order to solve the system of equations, the parameter space must be reduced either by introducing additional data, reparameterizing the parameter space, or by placing a restriction on the existing parameters. In this paper, the parameter space is reduced by reparameterizing into three distinct combinations of the original parameters:

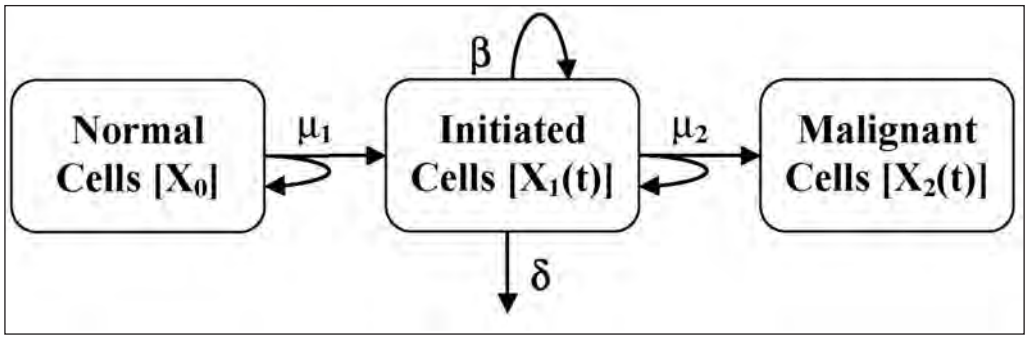

Fig. 1. The two-stage clonal expansion model where μ_1 is the mutation rate of normal cells (per unit time); μ_2 is the mutation rate of initiated cells (per unit time per cell); β is the birth/replication rate of initiated cells (per unit time per cell) and δ is the death/differentiation rate of initiated cells (per unit time per cell)

$$1)\ \psi = \beta - \delta - \mu_2$$
$$2)\ \rho = \mu_1 \mu_2$$
$$3)\ \eta = \frac{\mu_1}{\beta}$$

and setting the differentiation rate equal to zero (δ=0).

The two-stage model can be described in terms of initiation, promotion and progression (or transformation). Increasing the probability of a normal cell undergoing a transformation into an initiated cell is referred to as initiation. Promotion is the increase in the number of initiated cells through clonal growth (increasing the difference between the replication rate (β) and the differentiation rate (δ)). The transformation from an intermediate cell to a malignant cell is referred to as progression. Determining which of the stage or stages in the model are affected by radiation will, in turn, help describe the modifying effect of fractionation.

The objective in this paper is to compare the Cox proportional hazards model with the two-stage clonal expansion model, to see how well they fit the data and what they say about the cancer dose effect of radiation. In doing this we look at what each model estimates for the relative biological effectiveness of neutron, and the dose rate effectiveness factor associated with low dose rates of radiation, and how these relate to values used in radiation protection.

Material and methods

Data

The JANUS programme at the Biological and Medical Research Division of the Argonne National Laboratory (ANL) compiled a database between 1970 and 1992 on the response of F_1 hybrid mice, the $B6CF_1$ (a cross between C57BL/6 x BALB/c mice), to external whole-body irradiation. Detailed information concerning the individual experiment designs, the animals' care and maintenance and radiation factors have been published previously[10, 11].

The data include a total of between 20,000 and 40,000 mice, depending on the level of pathology. The mice were either controls or exposed to ^{60}Co γ rays or fission neutrons (mean energy 0.85 MeV) over a range of predetermined total doses calculated in centigray (cGy) at the midline of the mouse. The basic patterns of exposure investigated were: single exposure, 24 once-weekly exposures and 60 once-weekly exposures. The average age at onset of exposure was 110 days, in order to study the biological consequences of occupational levels of exposure to radiation on young adult animals. The mice were followed for the duration of their natural lives, at which point pathology judgements based on macroscopic examinations (autopsy) were used to determine the cause of death; furthermore a subset of these animals were selected at random to undergo a histological examination (microscopic)[10]. Comparisons of the macroscopic and microscopic pathology records for primary tumours causing or contributing to death are in agreement 98% of the time[11]. This suggests that the macroscopic data, with its larger sample size, can be used reliably for the analysis of these endpoints.

For the analyses in this paper, we used all of the dose groups of the JANUS data (Table 1) to examine the doses of gamma and neutron exposures and the effects of fractionating the exposure. Previously[12] a restricted subset neutron ≤30 cGy and gamma ≤300 cGy had been analyzed with respect to total tumour mortality.

Statistical methods

On average, the control mice and the mice with lower exposure doses lived longer than the mice exposed to higher irradiation doses (Table 1). Therefore, for the purpose of comparing the different exposure patterns and dose groups, it is necessary to truncate the populations at a point in time at which there are still some mice alive in all of the exposure groups. For these analyses, we used a cut-off point at 850 days (approximately 28 months) with any tumours occurring after this date treated as censored.

Table 1 - Summary of the mice included in the analyses: exposure pattern, dose (cGy), number of mice, mean age at death, number of cases of solid tumours and lymphoreticular tumours and percent

Exposure pattern	Dose[a]	Number of mice	MAD[b] Age	(±SE)	Cancer cases ST[c]	%	LRT[d]	%
Single gamma exposure	0	713	967.76	(± 7)	326	46	209	29
	86	571	940.95	(± 8)	287	50	157	27
	137	150	947.18	(±17)	71	47	43	29
	198	308	923.68	(±11)	150	49	112	36
	257	179	837.67	(±14)	77	43	61	34
	400	117	864.03	(±17)	49	42	38	33
	546	118	758.68	(±21)	34	29	40	34
	756	184	593.42	(± 9)	31	17	60	33
60 once-weekly gamma exposure	0	858	990.01	(± 7)	385	45	351	41
	100	562	979.45	(± 7)	233	42	275	49
	200	164	967.52	(±13)	67	41	72	44
	300	76	924.26	(±21)	30	40	38	50
	450	82	906.99	(±20)	31	38	39	48
	600	80	908.15	(±20)	33	41	40	50
	1839	139	757.01	(±12)	52	37	50	36
Single neutron exposure	0	1725	971.39	(± 5)	499	29	741	43
	1	661	987.82	(± 8)	181	28	320	48
	2	411	973.04	(± 9)	124	30	190	46
	5	312	949.01	(±12)	102	33	120	39
	9	230	931.75	(±13)	83	36	77	34
	19	780	892.80	(± 7)	296	38	276	35
	38	142	869.21	(±16)	69	49	45	32
	75	185	788.67	(±14)	63	34	47	25
	151	117	759.60	(±17)	53	45	28	24
	226	187	697.38	(±13)	54	29	35	19
60 once-weekly neutron exposure	0	705	991.22	(± 7)	187	27	399	57
	2	520	986.84	(± 8)	134	26	295	57
	8	204	975.03	(±11)	58	28	115	56
	14	219	924.02	(±11)	71	32	110	50
	22	225	912.86	(±11)	65	29	128	57
	31	135	905.47	(±14)	45	33	64	47
	41	76	837.08	(±18)	32	42	29	38
	151	152	742.46	(± 9)	68	45	41	27

[a] Total accumulated dose measured in cGy
[b] Mean age at death given in days plus or minus the standard error (± SE)
[c] Solid tumours
[d] Lymphoreticular tumours

Dose-response analyses were performed to examine the shape of the dose-response function for each exposure pattern. Of interest in these analyses are lymphoreticular tumours "all leukaemias and lymphomas" and solid tumours "all cancers other than leukaemia and lymphoma", where "tumour" is defined as a tumour that is determined to have caused or contributed to the death of the mouse. The results were generated using two different models.

The first model is the Cox proportional hazards model[13];

$$\lambda(t \mid D) = \lambda_0(t) \exp [\beta' D],$$

where t, the time variable, is the days at risk, D is a function of the total accumulated dose treated as a continuous variable, $\lambda(t \mid D)$ is the hazard function at time t given dose D for a mouse, $\lambda_0(t)$ is the unspecified baseline hazard function, and $\exp[\beta' D]$ is the relative risk.

To determine the function of dose to be used in the final model, four forms of dose were considered:

1) linear (D = dose),

2) quadratic ($D = dose^2$),

3) linear-quadratic, $\left(D = \begin{bmatrix} dose \\ dose^2 \end{bmatrix}\right)$, and

4) log-linear (D = log(dose)).

Each form of dose was modelled for each exposure pattern to determine how well they described the data. The Akaike Information Criterion (AIC)[14] was used to evaluate the least squares fitting to the models and determine which was the most appropriate function of dose to use in the model.

The second model is the two-stage clonal expansion model; since the parameters (θ) take on only positive values, they are modelled in the log-linear form so that

$$\log(\theta) = a + bD,$$

where D is the total accumulated gamma or neutron dose given to the mouse, a is a constant term, and b is the regression coefficient. The maximum likelihood estimates (MLE) of the parameters are estimated for the conditional likelihood function, using a simple transformation of the chain rule. Next, these values are converted into the original parameter values. More details on this method are available in Nakamura and Hoel[15].

To graphically examine and compare the result of the cumulative hazard estimates from the models discussed above, Kaplan-Meier estimates (K-M) of the observed hazard were also calculated for each exposure pattern and dose group as a reference.

Results

The results of evaluating the possible forms of dose for each exposure pattern in the Cox proportional hazards model are presented in Table 2, with the lowest AIC score marked in boldface. In all cases of gamma exposure, irrespective of cancer end-point or dose range, the AIC score was smallest for the linear form of dose, indicating that the linear model was the best fit or was indistinguishable from the other forms of the model, while for neutron exposure the model was dependent on the dose range used in the analyses. As with gamma exposure the linear model provided the best fit when the doses range was restricted to lower doses (i.e. <30 cGy), but the linear-quadratic model fit better for the entire dose range. This finding is consistent with previous life-shortening studies that found the dose-response curve to be linear for neutrons less than 10-50 cGy (depending on the dose-rate) and for the entire range of gamma irradiation[16-19]. Although the AIC score for linear dose in lymphoreticular tumours was slightly smaller than the linear-quadratic, the results were not significantly different. Therefore, subsequent references to the Cox proportional hazards model will be in reference to the linear form of the model for all low dose models, the entire range of gamma exposure models, and the linear-quadratic model for neutron exposure for the full dose range.

Radiation can affect the initiation rate, promotion rate, progression rate, or any combination of these three rates in a linear, quadratic or linear-quadratic manner. Therefore, there are six dose-related parameters considered in selecting the optimal model. To determine which of the parameters to include in the model, a stepwise selection procedure in which log likelihood was used to determine the best model at each level of parameter was conducted, and then a likelihood ratio test was performed, to see if the additional parameters significantly improved the fit of the model.

The best model to describe all of the exposure patterns for the low dose data subset is the model in which μ_1 is the only parameter directly affected by dose. Although for most exposures the other parameters did not behave significantly worse, the μ_1 model was consistently the better model. The slope coefficient of $\log(\mu_1)$ is positive for all exposure patterns, indicating an increase in the mutation rate with increasing dose. The models used to describe the entire dose range are more complicated, and in most cases, require more parameters (quadratic terms) to describe the data. The parametric forms of the models and the regression coefficients are presented in Table 3. The fractionated gamma exposure models were the exception, fit best by the linear promotion model (β is the only dose-dependent parameter in the model). For the other exposure patterns and cancer-endpoints the models suggest that there are both initiation and promotion effects in the radiation-induced carcinogenesis.

Plots of the log risk *versus* total accumulated dose are used to depict the shape of the dose-response curve for each cancer type and exposure pattern (figs. 2, 3) over the entire dose. In fig. 2, solid tumour, the Cox proportional hazards model (—) estimates the relative risk, while the two-stage model (---) estimates the absolute risk. Therefore, for comparison purposes, without affecting the meaning of the curves, the relative risk curves are adjusted to the absolute risk for the control group (dose = 0). The Kaplan-Meier observed risk (•) and the 95% confidence interval are plotted for each dose group as a reference. Fig. 3 is a similar plot for the lymphoreticular tumours.

The neutron dose-response curves indicate that at doses between 40 and 50 cGy, the neutron dose-response curve starts to bend downward due to the effect of the negative quadratic term in the models. The dose effect of

Table 2 - Akaike Information Criterion (AIC) Scores for the various forms of dose explored in the Cox proportional hazards model for each exposure pattern

Radiation quality	Exposure pattern	AIC Score			
		L[a]	Q[b]	L-Q[c]	L-L[d]
Lymphoreticular tumours					
Gamma	Single	**5992.56**	6001.42	5993.73	6076.81
	Fractionated	**6084.90**	6091.28	6086.12	6121.56
Neutron	Single	**16361.78**	16368.85	16362.97	16369.14
	Fractionated	9184.90	9195.69	**9178.91**	9184.19
Solid tumours					
Gamma	Single	**9003.20**	9006.17	9005.18	9012.18
	Fractionated	**5821.11**	5825.14	5822.95	5851.47
Neutron	Single	**12917.45**	12983.81	12858.12	12925.62
	Fractionated	4907.53	4932.34	**4893.50**	4927.85

[a] Linear
[b] Quadratic
[c] Linear-quadratic
[d] Log-linear

Table 3 - Parameter estimates from the two-stage clonal expansion model for each exposure pattern and dose range examined**.** Each parameter is modelled as $\log(\theta) = a + b_0 D + b_1 (D^2/100)$

Exp[a]	Cancer types	$\log(\mu_1^*)$			$\log(\beta^*)$			$\log(\mu_2^*)$		
		a^*	b_0	b_1	a	b_0	b_1	a	b_0	b_1
G1[b]	LRT[c]	-5.2876	—	0.00005	-4.8130	—	-0.00023	-13.0443	—	—
	ST[d]	-5.6721	0.00280	—	-4.6858	-0.00050	—	-12.0836	—	—
G60[e]	LRT	-5.3706	—	—	-4.7312	0.00023	—	-12.7190	—	—
	ST	-5.3483	—	—	-4.7485	0.00021	—	-12.6992	—	—
N1[f]	LRT	-5.4542	0.03107	-0.0071	-4.7575	-0.00600	—	-12.3611	—	—
	ST	-4.9557	0.02547	-0.0082	-4.9682	—	—	-12.5299	—	—
N60[g]	LRT	-5.2419	—	—	-4.6491	0.00545	-0.0024	-13.0251	—	—
	ST	-5.4325	0.00585	—	-4.8658	0.00815	-0.0036	-12.7533	—	—

[a] Exposure Patterns
[b] Gamma Single
[c] Lymphoreticular tumour
[d] Solid tumour
[e] Gamma Fractionated
[f] Neutron Single
[g] Neutron Fractionated
(—) value for a parameter indicates that that parameter was not included in the model

a single exposure to neutrons is less noticeable for lymphoreticular tumour (fig. 3C), the slope is not as steep and only the two-stage model indicates a bend, but not until higher doses (80 to 90 cGy); the Cox proportional hazard model is linear.

Dose rate and RBE

There are two measures that are used in the literature to describe the effects of different radiation quality and dose-rates: relative biological effectiveness (RBE) and dose rate effectiveness factor (DREF). The RBE, as defined in the Biological Effects of Ionizing Radiation (BEIR V)[20] is the biological potency of one radiation as compared with another to produce the same biological endpoint. The DREF is a factor by which the effect caused by a specific dose of radiation changes at low compared to high dose rates[20]. The DREF used is similar to the dose and dose rate effectiveness factor (DDREF) used by ICRP[1] and UNSCEAR[21] when it is assumed that at low doses the cancer effect is linear in dose.

It is well established in the literature that high-LET (linear energy transfer) radiations have greater biological effectiveness than low-LET radiations[22,23]. The problem is that the evidence suggests that there is no one RBE value for neutrons, because the RBE value is dependent on the

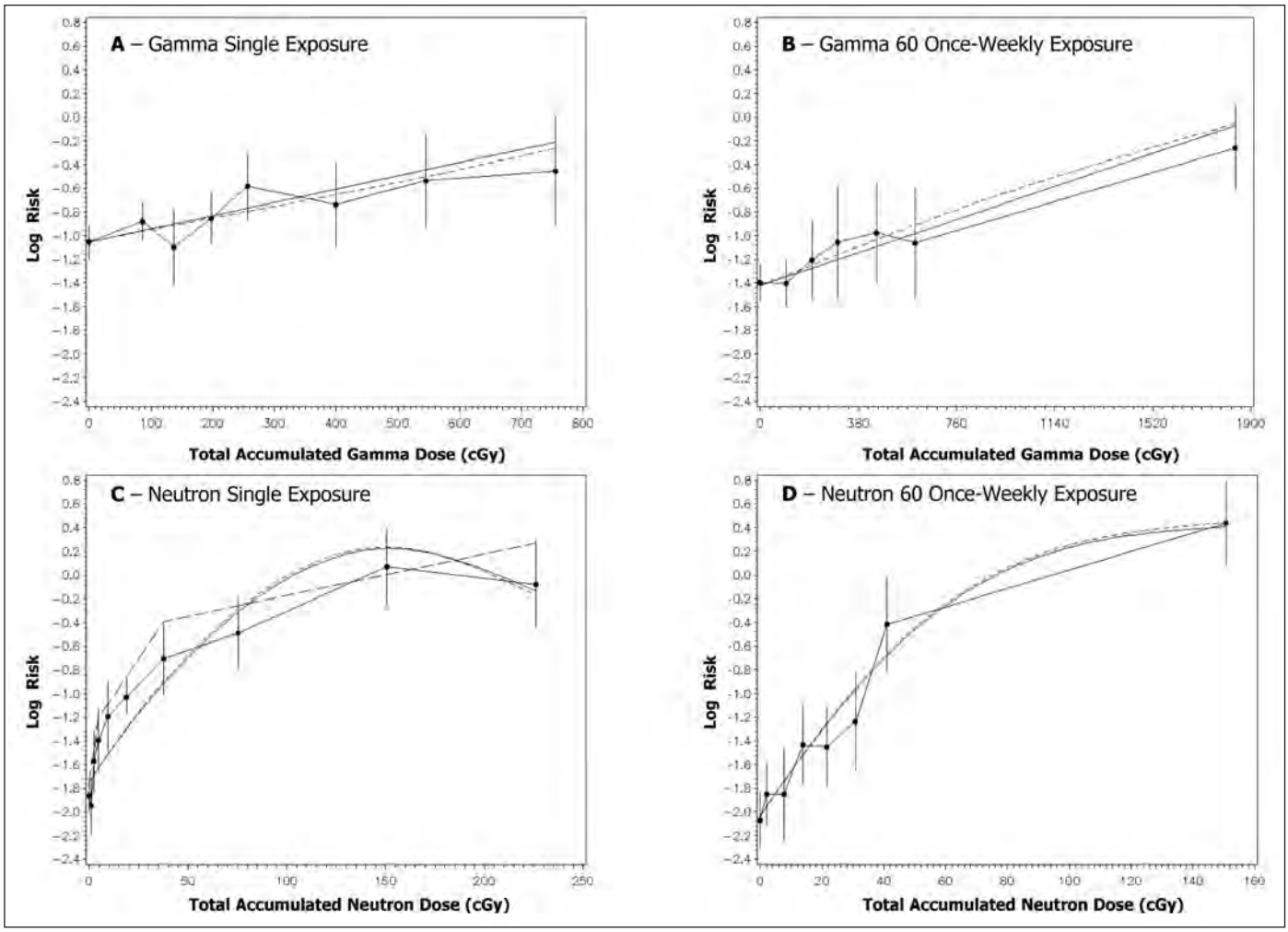

Fig. 2. Plots of log (risk) of solid tumours for each exposure group. Cox Proportional Hazards (CPH) plots of the relative risk (—), Two-Stage Clonal Expansion Model (TSM) plots of the absolute risk (---), and the Kaplan-Meier plot of the observed risk (•) for each dose group (with 95% confidence intervals)

dose, dose-rate, energy, fractionation, target tissue, and time[24]. The neutron-relative biological effectiveness is calculated as the ratio of the linear slope coefficients of the neutron and the reference radiation[25], in this study ^{60}Co gamma,

$$\mathrm{RBE} = \frac{\alpha_n}{\alpha_\gamma} \quad \text{with} \quad \mathrm{SE(RBE)} = \frac{1}{\alpha_\gamma}\sqrt{\sigma_n^2 + \frac{\alpha_n^2}{\alpha_\gamma^2}\sigma_\gamma^2},$$

where σ_γ^2 and σ_n^2 are the variance estimates of the slope coefficients. The RBE estimates and standard errors are presented in Table 4. The two models indicate similar patterns in the RBE estimates, with values ranging from 1.41 to 23.77 for acute exposure and 24.98 to 46.35 for fractionated exposures. An increase in RBE with fractionation is largely due to the reduction in the effectiveness of gamma with increased fractionation. These values are consistent with values obtained from previous studies, which have ranged from 2 to 100 depending on dose, dose-rate, energy, cell or tissue culture, and cancer endpoint. As seen in previous life-shortening studies the RBEs for lymphoreticular tumours are generally lower than those for some subtypes of solid tumours, and the

Table 4 - Estimates of the neutron-relative biological effectiveness and standard error for lymphoreticular and solid tumours for each model and exposure pattern

Model	Exposure pattern	Lymphoreticular		Solid tumour	
		RBE[a]	SE[b]	RBE	SE
CPH[c]	Single	1.49	0.25	22.46	4.66
	Fractionated	24.98	6.22	46.35	10.35
TSM[d]	Single	1.41	0.18	23.77	3.90
	Fractionated	25.02	5.26	43.95	8.52

[a] Relative biological effectiveness
[b] Standard error
[c] Cox proportional hazards model
[d] Two-stage clonal expansion model

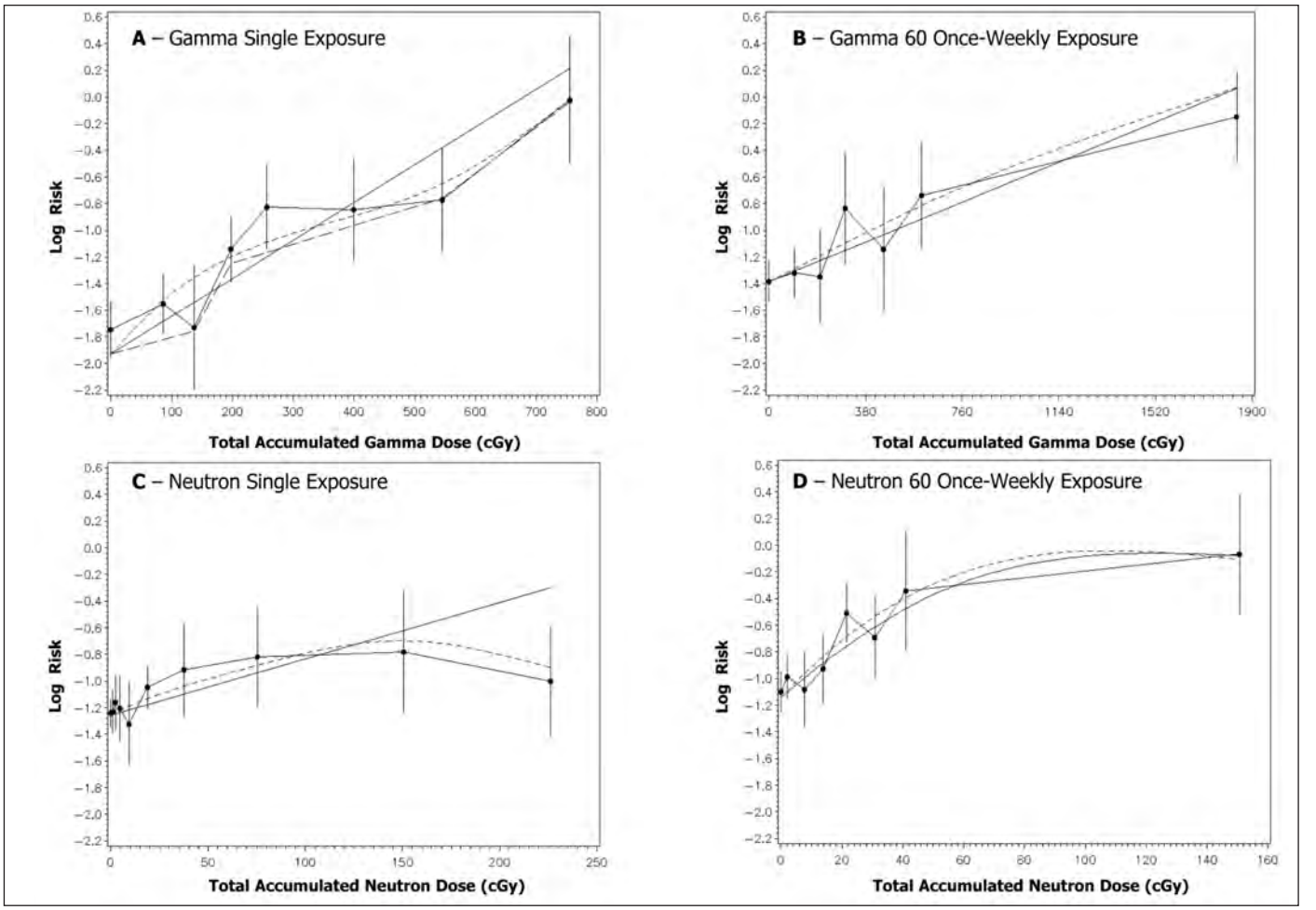

Fig. 3. Plots of log(risk) of lymphoreticular tumours for each exposure group. Cox Proportional Hazards (CPH) plots of the relative risk (—), Two-Stage Clonal Expansion Model (TSM) plots of the absolute risk (---), and the Kaplan-Meier plot of the observed risk (•) for each dose group (with 95% confidence intervals)

values for acute exposure are smaller than those for fractionated exposures due to the change in effectiveness with fractionation[17].

To compare the effectiveness of different dose rates for equal doses, DREF is used as described above. To estimate the DREF, we fitted data obtained at high and low dose rates separately (single and fractionated exposure) and used the estimated slope coefficients to calculate the DREF as

$$\mathrm{DREF} = \frac{\alpha_s}{\alpha_f}\left(1 + \frac{\sigma_f^2}{\alpha_f^2}\right)$$

$$\mathrm{SE(DREF)_U} = \frac{\alpha_s}{\alpha_f - c} \text{ and } \mathrm{SE(DREF)_L} = \frac{\alpha_s}{\alpha_f + c}$$

where $$c = \sqrt{\alpha_f^2\left(\frac{\sigma_f^2}{\alpha_f^2} + \frac{\sigma_s^2}{\alpha_s^2}\right)}.$$

In Table 5, the DREF for gamma and neutron irradiation are given for each cancer endpoint investigated. In general, the two-stage model and Cox proportional hazards model give similar results for gamma and neutron DREF for each of the cancer sites. Fractionation reduces the effectiveness of gamma response, but increases the effectiveness of neutron exposure (at doses greater than 40 cGy) similar to the findings from previous studies on life shortening[17], tumour mortality[26], and neoplastic transformations[27]. This differs from the analysis restricted to low dose where there was no notable difference in effectiveness of neutron exposures, which would be expected if the increase in effectiveness is seen at higher doses. The DREF estimate for lymphoreticular tumours is an example where the two-stage model, which is larger, and the Cox proportional hazards model do not produce similar results. This is due to the curvilinear nature of the two-stage model (fig. 2A).

The estimates of relative risk for each exposure pattern and model are presented in Table 6, with the estimates calculated for total accumulated doses of 100 cGy (1 Gy) gamma exposure and 10 cGy neutron exposure. The most

Table 5 - Estimates of the dose rate effectiveness factor and the Upper and Lower standard error for lymphoreticular and solid tumours for each model and radiation quality

Model	Radiation quality	Lymphoreticular		Solid tumours	
		DREF[a]	(U, L)[b]	DREF	(U, L)
CPH[c]	Gamma	3.65	(3.19,4.15)	1.53	(1.23,1.95)
	Neutron	0.22	(0.17,0.30)	0.65	(0.51,0.82)
TSM[d]	Gamma	5.76	(5.33,6.22)	1.22	(1.03,1.43)
	Neutron	0.29	(0.25,0.35)	0.68	(0.56,0.80)

[a] Dose rate effectiveness factor
[b] Upper and lower values for one standard error from the estimate
[c] Cox proportional hazards model
[d] Two-stage clonal expansion model

Table 6 - Relative Risk estimates of 100 cGy gamma or 10 cGy neutron radiation exposure for the Cox proportional hazards model and the two-stage clonal expansion model

Exposure pattern	Model	Relative Risk estimate	
		Lymphoreticular	Solid tumours
Gamma Single	CPH[a]	1.33	1.12
	TSM[b]	1.57	1.11
Gamma Fractionated	CPH	1.08	1.08
	TSM	1.10	1.09
Neutron Single	CPH	1.07	1.27
	TSM	1.07	1.28
Neutron Fractionated	CPH	1.21	1.44
	TSM	1.26	1.46

[a] Cox proportional hazards model
[b] Two-stage clonal expansion model

notable discrepancy in risk estimate is for the risk of lymphoreticular tumours from acute exposure to gamma irradiation, where the two-stage model estimates a 70% larger relative risk at 100 cGy exposure. This is due to the curvilinear nature of the two-stage dose response model: at 450 cGy the results are approximately reversed and the Cox proportional hazards model estimates a 70% larger risk than the two-stage model.

From the risk estimates we see that there is very little risk from highly fractionated gamma exposures, which agrees with the findings of the Canadian fluoroscopy study for lung cancer mortality[28]. This is interesting because the majority of the solid tumours in the JANUS data are lung cancers. The relative risk estimates based on the mortality studies of the A-bomb survivors[29] are risk estimates for an acute exposure to a combination of neutron and gamma irradiation, but at doses of 1 Gy the exposure is predominantly gamma rays. The estimated relative risk by gender for solid tumours was 1.17 (male) and 1.44 (female), these values are comparable to the gamma single exposure in our study (which are male mice, e.g. 1.12).

Discussion

The analyses performed in this paper were on mice exposed to single or fractionated doses of fission neutron or ^{60}Co gamma rays. The K-M estimates indicate that there may be some form of non-linearity in the low dose region of the acute gamma exposure. However, the confidence interval of the K-M estimate was large; and without data for doses between 0 and 86 cGy, it is impossible to discern it from a linear model. This unfortunate gap in the data affects our ability to definitively address the issue of linearity in the low dose region of the gamma dose-response curve.

In most cases the Cox proportional hazards model and two-stage clonal expansion model result in similar dose response curves, risk estimates, and weighting factors to describe the effect of radiation qualities and dose rates. But there are advantages of using a biologically-based model, such as the two-stage clonal expansion model: they necessitate a better understanding of the disease process being studied, the parameter estimates have biological interpretations, and they increase the credibility of the risk assessment[30].

It has been generally accepted that the majority of the biological consequences associated with ionizing radiation are due to a direct interaction with DNA, altering the replication and repair process. There are many types of radiation-induced DNA lesions, but misrepaired double strand breaks are considered the essential lesion in the induction of both chromosomal abnormalities and gene mutations[31]. Of these chromosomal abnormalities and gene mutations it has been suggested that the inactivation of a tumour suppressor gene, by loss of heterozygosity, is most likely to be the initiating event in radiation carcinogenesis[32].

For single exposures to gamma and neutron irradiation we see a positive initiation effect combined with a negative promotion effect. It has been hypothesized that in the presence of a strong initiator, such as radiation, an increase in apoptosis would accompany the increase in initiated cells due to initiation, in order to keep the number of intermediate cells in check[15].

The results for most cancer types and exposure patterns indicate that part of the risk from exposure to radiation is its effect on the net proliferation rate, a

promotion effect. Although it has been suggested that it would not be biologically plausible for a brief exposure to induce the increased growth imbalance necessary to see a promotion effect, it has been proposed that radiation inactivates or kills cells, which are then replaced by the division of neighbouring cells. Since initiated cells have a growth advantage over normal cells, they fill the void faster than normal cells[33].

The brief exposure periods experienced by the animals in the JANUS programme are quite different from the extended exposure periods used to define chemical carcinogenesis. Therefore a biological rationalization is needed to explain how radiation can cause a change in the parameter values that is constant throughout the entire study period. Recent studies have indicated that radiation may induce some indirect genetic consequences in cells that do not themselves receive direct nuclear radiation. Currently three areas of research into this phenomenon are: radiation-induced genomic instability, bystander effect, and cytoplasmic irradiation. The term genetic instability is used to describe a transformation, characteristic of a mutagenic event, which may occur in the progeny of an irradiated cell, even after many generations of cell replication. This leads to the hypothesis that radiation induces a transmissible genetic instability that has the effect of enhancing the rate of transformation in the descendants of an irradiated cell[32,34]. Bystander effect implies that persistent, genetic alterations can occur in nonirradiated cells due to damaged signals transmitted by neighbouring irradiated cells[32]. Furthermore studies have been demonstrated links between a bystander effect and genomic instability; chromosomal instability has been detected in the progeny of nonirradiated cells[35]. Cytoplasmic irradiation has been shown to induce a significant increase in the spontaneous mutation frequency, while having little effect on cell survival. These phenomena could play important rôles in the carcinogenic effects at lower doses, where fewer cells are in direct contact with the radiation[36] and would increase the probability that a cell could accumulate the mutational events necessary to give rise to a malignant tumour[37, 38]. These findings indicate that the carcinogenic effects of ionizing radiation are not restricted to the direct interaction with DNA and suggest that radiation could act as a chronic exposure.

There is a noticeable downward curvature at higher doses of the dose-response curves for neutron exposure. This type of curvature has been seen in this and other mouse data for life-shortening effects[16] as well as in the atomic bomb survivorship data[39]. Cell killing is the likely explanation of the downward curvature at higher doses. It has been shown that a linear model with an exponential cell killing term can be used to describe a linear-quadratic model, where the negative quadratic term indicates cell killing. Although this cannot be estimated directly by the Cox proportional hazards model, it provides an adequate fit to the Cox dose-response curve. The two-stage clonal expansion model does not include a parameter for cell killing and therefore it is not possible to separate the effects of cell killing from the other effects estimated in the model.

Inferences made about the mechanism of actions of an agent based on these analyses must be taken cautiously, because, although the two-stage model is useful in generating hypotheses about the underlying mechanism of carcinogenesis, it has been shown that tumour incidence data may not have the power to distinguish between initiating and promoting effects[40].

Conclusion

These analyses suggest that the empirical and biologically-based models result in similar, linear descriptions of the low-dose region of the dose-response curve. The difference in the two models is seen for single exposures to gamma irradiation with respect to lymphoreticular tumours in which the two-stage clonal expansion model predicts a steeper initial slope of the dose-response curve, and therefore a higher DREF and risk of cancer than the Cox proportional hazards model. The parameterization of the two-stage model suggests both the initiation and promotion effects are involved in radiation-induced carcinogenesis.

When the entire dose range is analyzed, the RBE for acute exposures is slightly lower than when one restricts the analysis to only the low dose data, while the fractionated exposures result in high RBE values. These values (RBE of approximately 23 for solid tumours and 1.5 for lymphoreticular tumours) are typical of the RBE values found in other studies, which have ranged from 2 to 100. The results suggest that neutron exposure appears to have more effect on solid tumours than gamma irradiation and a very small effect on lymphoreticular cancers. The DREF values indicate a reduction in the effectiveness of gamma irradiation with fractionation (DREF values 1.53-3.65 and 1.22-5.76 for the Cox proportional hazards model and two-stage model, respectively), while the neutron irradiation indicated an increased effectiveness when the entire dose range is analyzed (0.22-0.65 for the Cox model and 0.29-0.68 for the two-stage model).

The resulting non-linearities in the dose-response curve become evident at higher doses, as has been seen in life-shortening studies. In particular the dose-response curves for the different cancer endpoints following

neutron exposure bend downward at higher doses, possibly indicating a cell killing effect. To determine the best approaches to radiation protection, the issue of non-linearity in the dose-response curve will have to be settled based on a better understanding of the radiobiology associated with radiation carcinogenesis.

Acknowledgements

This research is supported by the funds from the US Department of Energy cooperative agreement DE-FC09-02CH11109 and by NASA grant NAG 9-1518.

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Eur. J. Oncol., vol. 11, n. 3, pp. 177-183, 2006

The rôle of stressful life events as risk factors in Italian patients with cancer: a case-control study

Il ruolo dei traumi psichici nella genesi dei tumori: uno studio caso-controllo

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Summary

***Objectives*. The aim of this study was to evaluate the risk of developing cancer in patients with a history of stressful life events. *Patients and methods*. 2,450 cancer patients were matched with 2,450 control subjects and their medical histories were reviewed for stressful life events such as bereavements, loss of parents during their youth, other stressful life events and multiple events. Confounding factors such as age, sex and smoking were considered. A logistic regression model was used for statistical analysis. *Results*. The overall adjusted odds ratio (OR) for developing cancer in subjects with a positive history for stressful life events is 1.23 (CI = 1.08-1.39). Bereavement (OR 1.52, CI = 1.23-1.87), other events (OR 1.59, CI = 1.28-1.99), and multiple events (OR 1.35, CI = 1.04-1.76) also revealed significant ORs. The OR was significant for subjects less than 30 years old (OR 3.33, CI = 1.38-9.71) and 51 to 70 (OR 1.2, CI = 1.02-1.41) years of age. *Conclusions*. Stressful life events contribute to the risk of developing cancer. This risk factor is more evident in young adulthood. Eur. J. Oncol., 11 (3), 177-183, 2006**

***Key words:* bereavement, cancer, stressful life events, risk factors, stress**

Riassunto

***Finalità*. Lo scopo di questo studio è stato di valutare il rischio di sviluppare un tumore in soggetti con anamnesi positiva per uno o più traumi psichici. *Pazienti e metodi*. Sono stati appaiati 2450 pazienti oncologici con 2450 controlli e sono state studiate le loro anamnesi per lutti, perdita dei genitori nell'infanzia, altri traumi psichici e traumi multipli. Sono stati considerati come fattori confondenti l'età, il sesso e il fumo. Si è utilizzato un modello di regressione logistica per l'analisi statistica. *Risultati*. L'*odds ratio* (OR) corretto di sviluppare un tumore in soggetti con anamnesi positiva per trauma psichico è di 1,23 (IC = 1,08-1,39). Il lutto (OR = 1,52, IC = 1,23-1,87), altri traumi (OR = 1,59, IC = 1,28-1,99), e traumi multipli (OR = 1,35, IC = 1,04-1,76) hanno rivelato un OR significativo. L'OR è inoltre significativo per soggetti con età inferiore ai 30 anni (OR = 3,33, IC = 1,38- 9,71) e nei soggetti nell'età compresa tra 51 e 70 anni (OR = 1,2, IC = 1,02-1,41). *Conclusioni*. I traumi psichici contribuiscono allo sviluppo dei tumori. Questo fattore di rischio è più evidente nei giovani adulti. Eur. J. Oncol., 11 (3), 177-183, 2006**

***Parole chiave:* lutto, tumori, traumi psichici, fattori di rischio, stress**

Received/Pervenuto 18.5.2006 - Accepted/Accettato 22.6.2006
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Introduction

The observation that stressful life events often precede the onset of diseases, and cancer in particular, is not new. Kowal[1] and LeShan[2], when reviewing the subject, reported consistent medical testimony, although anecdotal, dating from Galen onwards in which doctors observed this phenomenon. In the late 19th Century the theory that stressful life events precede cancer occurrence received greater weight from the observations of patients with breast cancer by Sir James Paget[3], and became a matter of heated debate.

Many aspects of the pathogenetic rôle of psychology in cancer have been studied. Some studies have examined the rôle of personality in subjects who developed cancer[4-7]; others have studied the rôle of depression[8-10], and still others have emphasized change in life situations as a possible cause of cancer observed in patients[11-13], with conflicting results[14-16].

More recently, advances in neuroendocrinology, immunology and psychology/psychiatry have led to the development of an interdisciplinary science known as psychoneuroimmunology. Psychoneuroimmunology can be defined as the study of interactions among neural, endocrine and immune processes of adaptation[17]. It implies a functional challenge to the complete autonomy of the immune system, and integrates the immune response within neuro-endocrine regulatory systems to fulfill a coordinated system of defence[18, 19]. Many aspects of the multiple circuits involved have been investigated, such as the anatomical connections between the autonomic nervous system and lymph node innervation[20], the effects of adrenocortical hormones on lymphocyte function[21], and the feedback circuit of cytokines secreted by the immune system to the Central Nervous System (CNS)[22, 23]. These effects have been correlated with mental states such as stress[24, 25], depression[10, 26, 27] or bereavement[28, 29], and their influence on the immune system has been observed[30]. The behavioural consequences of stressful life events have often been described in psychiatric studies, but a connection between these and the neuroendocrine and immunological changes leading to the onset of cancer have not been proven. Because of the difficulties involved in proving the psychoneuroimmunology theory in a clinical setting, studies have focussed on the occurrence of stressful life events in subjects who developed disease, in this case cancer, and have attempted to establish a statistical relationship between the two. However, while some studies have found an increased risk of developing cancer in subjects with stressful life events[31-35], others did not[14, 36, 37] and the debate has often been focussed on the association between stressful life events and the occurrence of breast cancer. To our knowledge the debate is still open in the scientific community. Our contribution to this debate will consider the rôle of a multiplicity of stressful events in a multiplicity of tumours because we believe that cancer is a highly individual process that will involve an individual's predisposition (psychological or physical) and will occur where the patient is somatically more vulnerable (due to genetic predisposition or environmental factors).

The aims of this retrospective case-control study are twofold: first, to evaluate the cumulative prevalence of stressful life events in subjects who have developed cancer, in order to investigate whether these events can be considered risk factors for cancer development. Secondly, to assess an eventual association between a single type of event in a patient's history and the onset of cancer.

Patients and methods

Patients

The medical records of 2,450 cancer patients (case subjects) who entered the Oncology Department at the Salvatore Maugeri Foundation and the Neurooncology Department at the Casimiro Mondino Neurology Foundation in Pavia, Italy between 1st October 1983 and 31st December 1997 were studied, as well as the medical records of 2,450 control subjects, matched for age and sex, hospitalized during the same period in other departments of the S. Maugeri Foundation and diagnosed with diseases other than cancer.

Study protocol

The medical records that were taken into consideration had to be complete in all aspects of the patient's medical history (family, physiological, and pathological) and had to contain the histological diagnosis of cancer for the case subjects. Medical histories in these hospitals are recorded in pre-defined, printed charts that record all aspects of a patient's medical history. These data are part of the routine examination that is undertaken when patients are hospitalized and were recorded before this study took place. Therefore neither the examiner nor the patient were aware of the hypotheses considered in this study.

The data collected from the cancer patients' files were:
- age of the subject when the first symptoms of cancer appeared;
- sex;
- type of cancer;

– presenting symptoms;
– the presence or absence of common risk factors for cancer, such as: smoking, a positive family history of cancer, chronic inflammation, infections predisposing towards cancer (such as hepatitis B or C), and previous radiation or chemotherapy for another cancer;
– the presence or absence of one or more stressful life events in the patient's history. In this study the following events were considered on the basis of traumatic events cited in the American Psychiatric Association DSM IV[38] and used in other studies[11-13]: 1) the death of a spouse, 2) the death of one or more children, 3) the death of a parent aged less than 50, 4) suicide or homicide of a close relative, 5) having been a prisoner of war, 6) divorce or separation, 7) one or more spontaneous or provoked abortions, 8) a spouse or a child having cancer, 9) an amputation of a visible body part due to an accident, or 10) having a combination of the above.

The different types of life events were grouped into four categories.

1) bereavements that included events number 1, 2 and 4;
2) the loss of one or both parents less than 50 years old (number 3);
3) other stressful life events, including events number 5, 6, 7, 8, 9;
4) multiple events that included a combination of the above (number 10).

Bereavements were separated from the other categories of stressful life events because studies on immunological function have documented a decrease in function during bereavement (of spouses in particular)[28]. The bereavement due to the loss of a parent was also considered separately from the other bereavements because it can be considered an event that occurred during the patient's childhood or in his adolescence (only the death of a parent less than 50 years old was considered separately).

The subjects were also divided into four age groups: 15 to 30, 31 to 50, 51 to 70, and above 70 years of age. These groups were formed using clinical criteria in order to reflect different processes (such as growth, middle life, accelerated ageing), and different frequencies in cancer incidence (more frequent in later years).

From the control subjects' medical records the following data were extracted:

– age;
– sex;
– the presence or absence of a common risk factor for cancer as cited above;
– the presence of one or more stressful life events as cited above.

Table 1 shows the demographic characteristics of the two populations and the distribution of common risk factors. Table 2 shows the types of cancer present in the case population and their frequency in this study.

Statistical analysis

A logistic regression model for matched data was applied to evaluate the odds ratio (OR) and relative 95% confidence intervals (CI). Estimates of the different ORs adjusted for smoking habits and other risk factors (autoimmunity) were also calculated. A model for unmatched data was also applied but did not significantly alter the results (data not shown).

Results

The results of this study are summarized in Table 3. The overall adjusted OR of developing cancer for a subject with a positive history of stressful life events in this study is 1.23 (95% CI = 1.08-1.39).

Subjects with a history of bereavement were more frequent among cancer subjects than among control subjects, and had an increased OR (adjusted OR = 1.52, 95% CI = 1.23-1.87) of developing cancer. This increase was also evident in those subjects with another stressful life event in their history (adjusted OR = 1.59, 95%

Table 1 - Demographic characteristics of the two populations under study

Subjects' characteristics	Cases	Controls
Sex		
M	1423	1423
F	1027	1027
Age (years)		
<30	70	70
31-50	572	572
51-70	1572	1572
>70	236	236
Somatic risk factors		
None	1121	1317
Smoking	1217	1072
Hereditary	18	8
Inflammatory	26	5
Infectious	4	25
Radio/chemotherapy	1	0
Combination	63	23
Total	2450	2450

Table 2 - Frequency of tumour types in the cancer population

Tumour type	No. of cases
1. Breast	449
2. Lung	404
3. Lower GIT[a]	263
4. Kidney+UT[b]	199
5. Upper GIT[a]	164
6. Oral	155
7. Upper RT[c]	117
8. Ovary	116
9. Lymphoma	102
10. Prostate	77
11. CNS[d]	58
12. Melanoma	57
13. Liver	55
14. Pancreas	40
15. Sarcoma	32
16. Uterus	27
17. Gall bladder	23
18. MM[e]	22
19. Pleura	21
20. CIN[f]	17
21. Testicle	16
22. Thyroid	12
23. Leukaemia	8
24. NOS[g]	16
Total	2450

[a] GIT = gastrointestinal tract; [b] UT = urinary tract;
[c] RT = respiratory tract; [d] CNS = central nervous system;
[e] MM = multiple myeloma; [f] CIN = cervical intraepithelial neoplasia;
[g] NOS = not otherwise specified

CI = 1.28-1.99) and in subjects with multiple life events (adjusted OR = 1.35, 95% CI = 1.04-1.76) whereas parental loss was more frequent in control subjects than in cancer patients (adjusted OR = 0.76, 95% CI = 0.62-0.94).

The importance of a history of stressful life events was also analyzed in the four age groups. Subjects between 15 and 30 years of age who had a stressful event in their history had cancer more frequently than peers who did not (adjusted OR = 3.66, 95% CI = 1.38-9.71). The OR was also significant in the 51 to 70 age group (adjusted OR = 1.2, 95% CI = 1.02-1.41), whereas it was no longer significant in the 31 to 50 age group (adjusted OR = 1.05, 95% CI = 0.8-1.39) or in the group above 70 years of age (adjusted OR = 1.42, 95% CI = 0.95- 2.13).

The confounding variables considered were smoking (which was the most frequent somatic risk factor for cancer in this study), and other somatic risk factors. The subjects were also stratified according to sex. The OR of stressful life events was increased in non-smokers (OR = 1.33, 95% CI = 1.18-1.5), and in subjects with other somatic risk factors (OR = 2.5, 95% CI 1.83-3.41). A history of stressful life events was more frequent in women (unadjusted OR = 1.18, adjusted for smoking and other risk factors OR = 1.27, 95% CI = 1.06-1.53) with respect to men (unadjusted OR = 1.29, adjusted for smoking and other risk factors OR = 1.18, 95% CI = 0.97-1.42).

Table 3 - Results: frequency of life events in cases and controls

	Informative couples		Odds Ratio	95%CI	Adjusted[a]	95%CI
Type of event	Case = 0 Control = 1	Case = 1 Control = 0				
Bereavements	179	242	1.45	1.18-1.76	1.52	1.23-1.87
Parental loss	242	174	0.79	0.65-0.96	0.76	0.62-0.94
Other events	142	223	1.65	1.33-2.05	1.59	1.28-1.99
Multiple events	118	146	1.38	1.07-1.77	1.35	1.04-1.76
Age (no. couples)						
15- 30 (n = 69)	6	20	3.33	1.35-8.18	3.66	1.38-9.71
31-50 (n = 572)	110	113	1.03	0.80-1.32	1.05	0.80-1.39
51-70 (n = 1572)	294	366	1.24	1.07-1.45	1.20	1.02-1.41
>70 (n = 236)	47	64	1.36	0.94-1.98	1.42	0.95-2.13
Gender						
Male	220	283	1.29	1.08-1.53	1.18	0.97-1.42
Female	237	280	1.18	0.99-1.40	1.27	1.06-1.53
Overall Odds Ratio					1.23	1.08-1.39

[a] The overall OR was adjusted for age, smoking habits and other somatic risk factors. The OR for age was adjusted for smoking and other somatic risk factors. The OR for gender was adjusted for age, smoking and other somatic risk factors

Discussion and conclusions

The method used in this study does not take into account the subject's personality or his/her capability of coping with a stressful event which can be considered subjective responses to stressful events. This information was unavailable for our study. We therefore limited our investigation to the presence or absence of a stressful event as an objective indicator. In doing this we can refer to a meta-analysis by Bennet-Herbert and Cohen[24] in which they argue in favour of using life events derived from objective data as being more stressful and more dependable than life events derived from subjective data; subjective data may be skewed in a retrospective study of this kind because of memory loss either in recalling the emotional reaction to a stressful life event or the different approaches a subject may have had to different stressful life events, and psychological distortions that may occur after a patient receives a diagnosis of cancer. Not all stressful life events could be considered, such as the loss of a job or of another significant relationship. However we believe the events chosen represent the most significant and frequently studied among stressful life events [11-13, 38].

The population of 2,450 cancer subjects presents many types of cancer. It has not been proven that stressful life events predispose a person towards a particular type of cancer rather than another; moreover, at least one study has discussed the possibility that subjects with a stressful life event may be predisposed towards the development of cancer in a site where a plurality of risk factors converges[39].

From this study, a subject who has one or more stressful life events in their history has an overall increased risk of developing cancer with respect to a subject who does not. This observation is in accordance with other studies[11, 12, 33]. Age was an important factor in this analysis. The marked increase in the probability of the occurrence of cancer observed during youth (under 31 years of age) is also supported by the scientific literature on this subject[27, 40-42] which underlines the importance of childhood stressful life events and parent-child relationships in the development of cancer. The OR for developing cancer is not significant in the 31 to 50 year age group and in subjects older than 70 years and this can be explained by attributing greater importance in this age group to other risk factors that could not be analyzed in this study. Somatic factors (genetic predisposition), environmental influence (viral infections, unhealthy dietary habits, smoking) and the ageing process could serve as confounding factors to a rôle played by stressful events. The OR is again modestly significant in the 51 to 70 year age group.

Among the different categories of stressful life events studied, bereavements alone seem more significant with respect to the other categories. This observation is also present in the scientific literature[28, 29, 43]. Bereavement may represent a situation in which a subject may feel impotent and unable to change the course of events, predisposing him towards being passive and unadaptive with regard to the necessary psychological changes needed. The experience of a particular type of bereavement, the loss of a parent in young age, is associated with a marked increase in the risk of developing cancer (OR= 3.66). In fact, the most frequent stressful life event in this age group was the loss of a parent. However this increase in the OR in adults is no longer evident (the adjusted OR for parental loss in adults is 0.76). This may be explained if one thinks of bereavement in youth as an all-or-nothing situation: if the subject copes with the stressful event, it will not influence his predisposition towards developing cancer in later life. If, however, the subject is unable to cope, the event assumes great importance to the subject's condition of health. In other words this particular risk factor is important during youth, but loses its importance with time depending on the subject's ability to cope with the bereavement.

The adjustment for age, smoking and other somatic risk factors has a different effect in females and in males. In particular the OR increases in females with adjustment whereas it loses its significance in males. Therefore it would seem that stressful life events have greater importance in females, whereas the confounding effect of age, smoking and other somatic risk factors is greater in males. The difference being small, this result could be due to sample variability.

One drawback of studying two populations at a given time is that it will remain unknown whether the control subjects with a positive history for stressful life events will have cancer in the future.

It is still unknown by which mechanisms the neuroendocrine system may influence the immune system in carcinogenesis, but it is generally believed that disregulation of the neuroendocrine system is responsible for a decrease in natural immune surveillance (deficient NK cell function) and lymphoproliferative response[44]. Subjects with persistent activation of the hypothalamic-pituitary-adrenal axis and the sympathetic-medullary-adrenal axis in chronic stress response have been found to have these immune impairments as well as high levels of acute phase proteins, specific herpes antibodies, and interleukins (especially IL-1, IL-6, TNF alpha) resulting in chronic inflammation and a shift in the Th1/Th2 balance[45]. This in turn influences the expression of oncogenes already activated in the cell by somatic mutation[46-48].

The impact of the occurrence of stressful life events on the neuroendocrine system and on the expression of oncogenes is still a matter of study[48]. Recently, research on histone modification and DNA methylation has brought to light how these processes influence tumour suppressor genes. More specifically, a dominant-negative point mutant of lysine H3-K27R, not yet studied, was overexpressed in a cell line to study its rôle in ovarian cancer. Expression of this construct caused a loss in methylation at H3-K27R, an overall reduction in DNA methylation and an increased expression of tumour suppressor genes, in particular RASSF1. Removal of H3-K27 methylation resensitized drug-resistant ovarian cancer cells to the chemiotherapeutic agent cisplatin[49].

Future research should evaluate prospectively the major types of stressful life events susceptible of predisposing towards cancer. To our knowledge few have been undertaken and have demonstrated a modest positive association of bereavement or stressful life events and cancer onset[50-52]. Assessing psychological, neurendocrine and immune function before, during and after a stressful life event could also be useful.

In conclusion this study supports the hypothesis that stressful life events may contribute to the risk of developing cancer especially during young adulthood, when the risk of bereavement causing cancer seems to be more evident.

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Eur. J. Oncol., vol. 11, n. 3, pp. 185-191, 2006

Il mesotelioma pleurico nei lavoratori esposti ad amianto nelle raffinerie di petrolio: malattia professionale ed evento sentinella

Pleural mesothelioma among asbestos-exposed workers in petroleum refineries: a work-related disease and a sentinel event

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Riassunto

***Finalità*. Prima dei nostri studi epidemiologici i lavoratori delle raffinerie di petrolio non erano considerati a rischio per patologie asbesto-correlate nonostante la documentata presenza di amianto. L'articolo riporta questi studi che evidenziano un elevato rischio di mesotelioma pleurico e segnalano l'origine professionale di alcune patologie asbesto-correlate tra i manutentori delle raffinerie. *Materiali e metodi*. Studi epidemiologici di coorte e caso-controllo condotti in Liguria e Canada hanno analizzato il sottogruppo maggiormente esposto ad amianto (manutentori) ed i gruppi di riferimento non esposti (impiegati e popolazione generale). Il rischio relativo (RR) ed il rischio attribuibile (RA) sono stati stimati anche tramite la regressione di Poisson. *Risultati*. I nostri studi sui manutentori hanno evidenziato un altissimo RA per mesotelioma pleurico (96-100%) e per tumore polmonare (42-49%) ed un eccesso di mortalità per il complesso delle cause neoplastiche e non neoplastiche. *Conclusioni*. L'eccesso di mesoteliomi (evento sentinella) ha permesso di identificare il gruppo esposto ad amianto (manutentori). Il confronto interno ha permesso di rilevare eccessi di patologie asbesto-correlate. La presenza di un rischio amianto in raffineria è ora confermata a livello internazionale, ma si tende a circoscrivere al solo mesotelioma gli effetti dell'amianto. Se-**

Summary

***Aim*. Before our epidemiological studies, petroleum refinery workers were not considered at risk for asbestos-related pathologies, in spite of the documented presence of asbestos. This article reports these studies, which demonstrate a high risk of pleural mesothelioma and point to the occupational origin of some asbestos-related pathologies among the maintenance staff of the refineries. *Materials and methods*. Cohort and case-control epidemiological studies, conducted in Liguria and Canada, analysed the subgroup most heavily exposed to asbestos (maintenance staff) and the control groups not exposed (office staff and the general population). Relative risk (RR) and attributable risk (AR) have been estimated also using Poisson regression. *Results*. Our studies on the maintenance staff have indicated a very high AR for pleural mesothelioma (96-100%) and lung cancer (42-49%), and an excess of mortality due to all neoplastic and non-neoplastic causes. *Conclusions*. The excess of mesothelioma (sentinel event) has permitted the identification of the group exposed to asbestos (the maintenance staff). The internal comparison has allowed the detection of excess asbestos-related pathologies. The presence of an asbestos risk in refineries is now confirmed at an international level, but there is a tendency to limit the effects of asbestos to mesothe-**

Received/Pervenuto 4.5.2006 - Accepted/Accettato 27.6.2006
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condo i nostri studi, invece, molte altre patologie neoplastiche e non neoplastiche dovrebbero essere riconosciute malattie professionali. Per evidenziare tali rischi è però necessario utilizzare metodi aderenti alla buona pratica epidemiologica, come l'identificazione del sottogruppo di soggetti realmente esposti e della corretta popolazione di riferimento. Eur. J. Oncol., 11 (3), 185-191, 2006

Parole chiave: **epidemiologia, raffinerie di petrolio, manutentori, malattia professionale, tumori, asbesto**

lioma only. On the contrary, according to our studies, many other neoplastic and non-neoplastic pathologies should be recognized as occupational diseases. In order to highlight such risks, it is however necessary to use methods which are in accordance with good epidemiological practice, such as the identification of both the subgroup of actually exposed workers and the appropriate reference population. Eur. J. Oncol., 11 (3), 185-191, 2006

Key words: **epidemiology, petroleum refineries, maintenance staff, occupational disease, cancers, asbestos**

Introduzione

Il rischio cancerogeno legato al lavoro nelle raffinerie di petrolio (RP) è stato valutato da alcuni studi epidemiologici condotti soprattutto negli anni '80. Basandosi su tali studi e sull'osservazione che in quell'ambiente erano state rilevate oltre 50 differenti sostanze tossiche, mutagene e cancerogene (tra cui amianto, arsenico, benzene, cromo esavalente, nichel, idrocarburi policiclici, silice, ecc.), nel 1989 l'Agenzia Internazionale per la Ricerca sul Cancro (IARC) ha classificato l'esposizione occupazionale nelle raffinerie di petrolio come probabilmente cancerogena (gruppo 2A), con particolare riferimento alle leucemie ed ai tumori cutanei[1].

Le prime evidenze epidemiologiche di uno specifico rischio amianto nelle RP sono emerse all'inizio degli anni '70 in Germania[2,3], mentre nel 1980 Lilis *et al*[4] hanno rilevato la presenza di casi di asbestosi. La prima indagine epidemiologica di coorte storica ha rilevato 9 decessi per mesotelioma pleurico (MP), con rischio aumentato del 140% (*Standardized Mortality Ratio* - SMR=2,41)[5]. Dopo questa segnalazione, il problema mesotelioma nelle RP è stato messo in evidenza a Genova[6,7] e confermato a La Spezia[8]. Nel 1996, Finkelstein[9] ha segnalato il problema dell'esposizione ad amianto anche nelle raffinerie del Canada. Tali evidenze sono state sostanzialmente confermate fino ad oggi[10].

In questo articolo si riportano i principali risultati della serie di studi condotti sulle due raffinerie della Liguria, che hanno provato, congiuntamente alle evidenze emerse nella fase di controllo della bonifica della ASL competente, l'esistenza di un'elevata esposizione ad amianto nelle RP e di un'elevata mortalità per mesotelioma pleurico e tumore polmonare tra i lavoratori delle RP. L'utilizzo del MP come evento-sentinella dell'esposizione ad amianto ha poi permesso di evidenziare altri rischi sanitari legati al lavoro nelle RP.

Questa sintesi degli studi fino ad oggi effettuati nelle due raffinerie della Liguria (Genova e La Spezia) ha l'obiettivo di confermare il nesso causale fra esposizione ad amianto nelle RP e varie conseguenze per la salute dei lavoratori.

Metodi

La coorte dei lavoratori della raffineria genovese[6,7] comprendeva 1.368 uomini che avevano lavorato nell'impianto almeno un giorno tra il 1949 ed il 1988; il relativo *follow-up* è stato aggiornato al 1991[8]. La coorte dei lavoratori della raffineria spezzina[8] comprendeva 931 uomini che avevano lavorato nell'impianto almeno un giorno tra il 1914 ed il 1977; l'ultimo *follow-up* è stato aggiornato al 1999[11].

La metodologia epidemiologica comune a tutti questi studi di coorte storica è stata quella di analizzare i lavoratori in base alla probabilità di esposizione, considerando gli impiegati come gruppo di riferimento interno anziché includerli nel gruppo a rischio, isolando poi il gruppo più probabilmente esposto ad amianto (i manutentori) dagli altri operai. Questa ultima operazione è stata purtroppo possibile solo nella raffineria spezzina.

I rischi di decesso per le principali cause di morte sono stati stimati calcolando sia l'SMR nei confronti della popolazione generale (nazionale e locale), sia il rischio relativo (RR) nei confronti del gruppo di riferimento interno (impiegati), che risulta il miglior gruppo di controllo essendo stato anch'esso sottoposto ad una selezione di idoneità per l'assunzione.

Risultati

Nel primo studio sulla raffineria genovese[6,7], le poche informazioni disponibili sulle mansioni avevano permesso di suddividere i dipendenti solo in due gruppi: operai ed impiegati/dirigenti. Nel periodo osservato, avevano lavorato per almeno un giorno 950 operai e 418 impiegati/dirigenti. È stato stimato un RR degli operai aumentato del 60% per tutte le cause e del 50% per tutti i tumori rispetto agli impiegati, mentre il rischio di decesso per tumore polmonare era aumentato del 90%. In quel primo studio erano stati osservati 3 casi di mesotelioma e 2 di leucemia: pochi casi, ma comunque superiori all'atteso.

Lo studio è stato poi aggiornato ed ampliato includendo la RP spezzina[8] ed è stata analizzata la mortalità nel periodo 1950-1991. Complessivamente, sono stati identificati 10 decessi per mesotelioma (5 fra i lavoratori di ciascuna RP). Analizzando separatamente le due raffinerie, è stato rilevato un rischio raddoppiato fra gli operai della RP spezzina rispetto alla popolazione della provincia stessa e aumentato di 14 volte rispetto alla popolazione italiana (Tabella 1). Analogo andamento era stato osservato nella RP genovese, dove il rischio era triplicato rispetto alla popolazione della provincia stessa ed aumentato di circa 19 volte rispetto alla popolazione italiana. L'anamnesi professionale ha permesso di scoprire che 7 soggetti avevano lavorato come manutentori e 1 come elettricista (per 2 soggetti non è stato possibile ricostruire la storia professionale).

Nonostante la standardizzazione della tecnologia e delle procedure applicate nelle RP a livello mondiale permettesse di escludere che le evidenze emerse da questi studi potessero essere peculiari delle raffinerie liguri, la segnalazione fu criticata[12], chiedendo, fra l'altro, come fosse possibile attribuire i casi di mesotelioma osservati all'esposizione ad amianto, dato che non era stato evidenziato alcun eccesso di tumore polmonare nelle stesse raffinerie, dimenticando che l'eccesso di tumori polmonari può essere opportunamente rilevato solo nel sottogruppo di esposti ad amianto.

Tabella 1 - Mortalità per mesotelioma pleurico tra gli operai in due raffinerie della Liguria[a]

Raffineria	Decessi osservati	Popolazione di riferimento	
		Provincia	Italia
		SMR[b] (IC[c] 95%)	SMR (IC 95%)
Genova	5	3,88 (1,26-9,04)	19,26 (6,24-44,87)
La Spezia	5	2,03 (0,66-4,73)	14,35 (4,65-33,44)
Totale	10	2,66 (1,28-4,89)	16,63 (7,97-30,58)

[a] Da Gennaro *et al*[8], modificata
[b] SMR = Standardized Mortality Ratio
[c] IC = Intervalli di Confidenza

A nostro parere, uno dei limiti dello studio, invece, era la bassa numerosità della coorte in esame (rispetto agli standard statunitensi), che ha permesso di rilevare solo 10 casi di mesotelioma. Inoltre, come in molti studi epidemiologici, non è stato possibile valutare direttamente l'effettiva esposizione. Questo inconveniente è stato, però, parzialmente superato grazie alla Unità Sanitaria Locale (USL) che, intervenendo nell'azione di bonifica e di smantellamento della raffinera di Genova, ha fornito dati oggettivi sulla presenza di amianto e quindi, indirettamente, sulla possibile pregressa esposizione dei manutentori. In particolare, è stato evidenziato che in vari settori era presente materiale rivestito di amianto e cemento-amianto (tubi, coppelle, ecc.)[13].

Sulla base delle evidenze riscontrate in questi primi due studi, ne sono stati condotti altri utilizzando il mesotelioma come evento sentinella per valutare il rischio di decesso per tumore polmonare ed altre patologie asbesto-correlate.

Per un primo studio è stato possibile suddividere i lavoratori della RP spezzina in sottogruppi più omogenei tra loro (manutentori, operai e impiegati), permettendo di evidenziare la differenza nel rischio asbesto-correlato tra lavoratori occupati negli uffici (cioè impiegati, non esposti), quelli addetti alla produzione (operai, gruppo ad esposizione intermedia) ed un sottogruppo di operai addetti alla manutenzione (esposti ad amianto). La distinzione fra manutentori e altri operai era basata proprio sull'osservazione che la maggior parte dei 10 decessi per mesotelioma pleurico osservati nei precedenti studi era stato rilevato proprio tra i manutentori[14].

Basandosi su questa prima stima delle differenti esposizioni ad amianto, i rischi per tumore polmonare fra i lavoratori della RP spezzina sono stati confrontati con quelli riportati in uno studio di Finkelstein[9], che in Ontario (Canada) aveva segnalato in maniera indipendente analoghe esposizioni ad amianto e relativi rischi asbesto-correlati in lavoratori delle RP.

Questo confronto ha evidenziato un rischio attribuibile (RA) per mesotelioma pleurico nei manutentori delle RP intorno al 96% sia in Liguria sia in Canada (rispetto alla popolazione delle rispettive regioni) (Tabella 2). Il RA nella RP italiana saliva al 100% quando i manutentori erano confrontati con gli impiegati. In entrambi i *set* di dati, il RR per tumore polmonare era aumentato nei manutentori: in Liguria del 97% (statisticamente significativo = ss, RA = 49%) e in Canada del 73% (non statisticamente significativo = nss, RA = 42%) rispetto al riferimento interno (impiegati e altri operai, rispettivamente) (Tabella 3). I risultati dei due studi sono quindi consistenti, nonostante le differenze riguardanti la metodologia applicata (studio di coorte in Italia e studio

Tabella 2 - Mortalità per mesotelioma nei manutentori delle raffinerie di petrolio italiana (I) e canadese (C): stima del Rischio Relativo (RR) e Rischio Attribuibile percentuale (RA), con i rispettivi Intervalli di Confidenza (IC)

Regione	Disegno dello studio	RR (IC)	RA (IC 95%)	Riferimento
Liguria (I)	Coorte	29,3 (9,5-68,3)[a]	96,6 (92,0-98,6)	Popolazione italiana
		-	100	Impiegati[b]
Ontario (C)	Caso-controllo	24,5 (3,1-102,0)[c]	95,9 (70,0-99,6)	Popolazione dell'Ontario

[a] Standardized Mortality Ratio (IC 95%)
[b] Nessun decesso è stato osservato in questo gruppo di riferimento
[c] Odds Ratio (IC 90%)

Tabella 3 - Mortalità per tumore polmonare nei manutentori delle raffinerie di petrolio italiana (I) e canadese (C): stima del Rischio Relativo (RR) e Rischio Attribuibile percentuale (RA), con i rispettivi intervalli di confidenza (IC)

Regione	N. decessi	RR (IC)	RA (IC 95%)	Riferimento
Liguria (I)	16	1,97 (1,13-3,20)[a]	49,2 (26,4-72,4)	Impiegati[b]
Ontario (C)	28	1,73 (0,83-3,60)[c]	42,2 (10,8-82,6)	Altri lavoratori

[a] Standardized Mortality Ratio (IC 95%)
[b] Inclusi gli impiegati della RP genovese descritta nel testo
[c] Odds Ratio (IC 90%)

caso controllo in Canada), la popolazione osservata, l'area geografica ed i periodi di esposizione ed osservazione.

È importante notare che sono stati rilevati tra 1,6 e 2,1 decessi per tumore polmonare attribuibili all'esposizione ad amianto per ogni decesso per mesotelioma osservato nelle due RP (Tabella 4).

Anche questo studio ha ricevuto inizialmente alcune critiche e commenti da parte degli epidemiologi delle raffinerie statunitensi[15, 16], che invece hanno ripetutamente pubblicato risultati tranquillizzanti perché significativamente ridotti, analizzando sempre l'insieme di tutti i lavoratori. Approfondendo l'analisi, nonostante la limitata dimensione della coorte ligure, è stato possibile osservare una chiara relazione dose-risposta in funzione sia della durata d'impiego sia della latenza (figg. 1, 2), con un rischio che aumentava maggiormente nei manutentori ri-

Tabella 4 - Stima del numero di decessi per tumore polmonare attribuibile ad amianto per ogni singolo caso di mesotelioma osservato nelle raffinerie studiate

Regione	Decessi attribuibili ad amianto	
	Tumore polmonare/mesotelioma	Rapporto
Liguria (I)	7,8/5	1,6
Ontario (C)	11,8/5,7	2,1

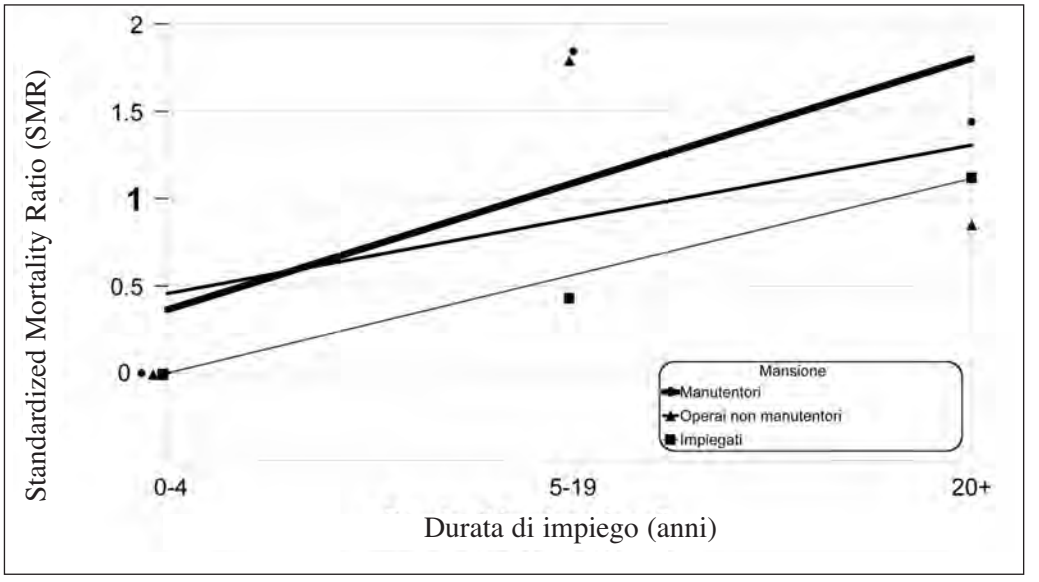

Fig. 1. Rischio di decesso per tumore polmonare per durata di impiego e categoria lavorativa (aggiornamento: 1999; riferimento: popolazione italiana)
Da Gennaro *et al*[17], modificata

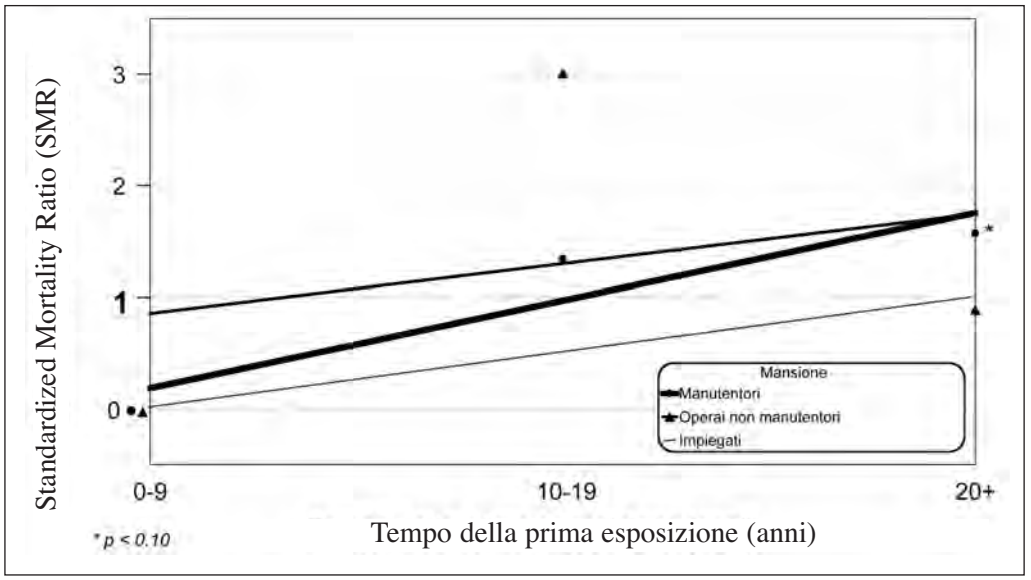

Fig. 2. Rischio di decesso per tumore polmonare per latenza e categoria lavorativa (aggiornamento: 1999; riferimento: popolazione italiana)
Da Gennaro *et al*[17], modificata

spetto agli altri gruppi di lavoratori (altri operai e impiegati)[17].

Le recenti evidenze inducono a non abbassare la guardia sul rischio amianto nelle RP. L'aggiornamento del *follow-up* della coorte spezzina al 1999 (Tabella 5) ha permesso di identificare ulteriori decessi per mesotelioma pleurico sia tra i manutentori (3) sia tra gli altri operai (1), ma non tra gli impiegati, impedendo di stimare puntualmente un rischio rispetto al riferimento interno, ma di fatto mantenendo al 100% il RA[11]. Sono stati anche identificati nuovi decessi per tumore polmonare sia tra i manutentori (8) sia tra gli operai (1) sia tra gli impiegati (3). Il nuovo RR per questa patologia dei manutentori rispetto al riferimento interno (impiegati), corretto per possibili variabili confondenti, è uguale a 1,53 (ss).

Il secondo rapporto del Registro Nazionale Mesoteliomi (ReNaM) riporta 31 casi di mesotelioma diagnosticati nel periodo 1993-2001 fra i lavoratori delle RP, segnalati dai Centri Operativi Regionali (COR) finora attivati[18].

Un *linkage*, eseguito nel 2003, tra il *database* del Registro Mesoteliomi della Liguria (COR Liguria)[19] e quello della coorte della RP spezzina ha segnalato 5 nuovi casi di mesotelioma pleurico diagnosticati dopo la chiusura del *follow-up* 1999. L'anamnesi lavorativa raccolta dal COR Liguria ha permesso di identificare le mansioni (3 manutentori, 1 operaio e 1 impiegato), le esposizioni ad amianto (4 certe, 1 non definita), la certezza della diagnosi di mesotelioma (4 certe con conferma istologica, 1 probabile). Tale *linkage* sarà ripetuto nel corso del 2006, includendo tutti i nuovi casi incidenti[20].

Tabella 5 - Numero di lavoratori (N), casi, persone-anno (PA) e Rischi Relativi (RR)[a] con Intervalli di Confidenza (IC) al 95%, tra i manutentori e gli altri operai nei confronti degli impiegati in una raffineria di petrolio[b]

	Riferimento (Impiegati) N = 221 (PA = 7.285)		Manutentori N = 357 (PA = 11.016)			Altri operai N = 353 (PA = 11.210)		
Cause di decesso (ICD IX)	Casi	RR	Casi	RR	IC 95%	Casi	RR	IC 95%
Tutte le cause (000-999)	118	1,00	196	1,12	0,95-1,33	175	1,01	0,85-1,20
Tutti i tumori (140-208)	34	1,00	74	1,50	1,18-1,90	51	1,01	0,78-1,30
T. dell'apparato digerente (150-159)	13	1,00	27	1,41	1,07-1,87	17	0,89	0,66-1,22
T. della laringe (161)[c]	0	-	1	-	-	0	-	-
T. del polmone (162)	11	1,00	24	1,53	1,11-2,10	17	1,04	0,75-1,46
T. della pleura (163)[c]	0	-	8	-	-	1	-	-
Malattie respiratorie (460-519)[d]	9	1,00	23	1,71	1,23-2,38	16	1,22	0,86-1,72
Malattie cardiocircolatorie (390-459)	48	1,00	58	0,82	0,66-1,02	74	1,05	0,86-1,29

[a] RR aggiustati per età, età alla diagnosi, periodo di calendario, durata di esposizione e latenza
[b] Da Montanaro *et al*[11], modificata
[c] Nessun caso rilevato nel gruppo di riferimento
[d] Include 2 e 8 decessi per pneumoconiosi tra gli operai ed i manutentori, rispettivamente

Discussione

I rischi sanitari dei lavoratori delle RP sono stati evidenziati con molto ritardo. Ad esempio, nella coorte di lavoratori studiata da Kaplan, era già stato evidenziato l'eccesso di decessi per MP ma anche una riduzione della mortalità per tutte le cause (SMR = 78, ss) e per tutti i tumori (SMR = 87, nss)[5]. Questo si è verificato in altre indagini sostenute dall'industria petrolchimica. Nella grossa metanalisi di Wong e Raabe[21] è stata addirittura segnalata una significativa riduzione del rischio di decesso per tumore polmonare (SMR = 0,77). Purtroppo, lo studio presentava alcune lacune difficili da rilevare per il lettore, come il breve periodo di osservazione (*follow-up*) dei lavoratori esposti che non ha permesso un appropriato studio degli effetti neoplastici (che solitamente compaiono dopo molti anni dall'esposizione), o come la mancanza di un'analisi multivariata, che tecnicamente permette di valutare i rischi senza il confondimento di molteplici fattori, oltre ai citati problemi legati alla scelta del riferimento ed alla selezione della popolazione in studio.

Simili studi hanno indotto a pensare che i lavoratori delle raffinerie fossero protetti o non esposti ad agenti nocivi, data la loro minor mortalità rispetto alla popolazione di riferimento. Data l'entità degli interessi in gioco, oltre alla oggettiva difficoltà nelle indagini, la maggior parte di questi studi è stata sostenuta dalle stesse multinazionali, mentre sono oggettivamente rare le ricerche condotte da strutture non legate all'industria che, come i nostri studi, sono riuscite ad evidenziare possibili rischi sanitari anche se basate su coorti di lavoratori più limitate. In particolare, si può ipotizzare che i casi di mesotelioma negli Stati Uniti non fossero studiati nel dettaglio ma inclusi tra gli "altri tumori" e non utilizzati come evento sentinella. Questo semplice accorgimento avrebbe permesso di individuare l'esposizione ad amianto e le connesse patologie di un'intera categoria lavorativa.

Conclusioni

Per meglio dimostrare possibili rischi legati all'esposizione lavorativa abbiamo ritenuto opportuno confrontare i lavoratori esposti con i lavoratori non esposti, che hanno subito un'analoga selezione d'idoneità fisica all'assunzione. Da questa indagine abbiamo evidenziato:

– la presenza di amianto nelle RP;
– la presenza di un gruppo di lavoratori esposti ad amianto (i manutentori);
– l'eccesso di decessi per mesotelioma pleurico e tumore polmonare tra i manutentori delle RP.

Con queste evidenze, emerse grazie ad un approccio più mirato, possiamo concludere che il mesotelioma deve, con ragionevole certezza, essere considerato:

– un tumore professionale nei lavoratori delle RP;
– un evento sentinella della esposizione ad amianto per l'identificazione di altre patologie asbesto-correlate;
– un evento sentinella di insufficiente protezione dei lavoratori esposti sia ad amianto, sia probabilmente ad altri agenti cancerogeni.

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Eur. J. Oncol., vol. 11, n. 3, pp. 193-199, 2006

Very large jejunal GIST. New diagnostic and therapeutic perspectives

GIST digiunale di grosse dimensioni. Nuove prospettive diagnostiche e terapeutiche

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Summary

The term GIST refers to a group of Gastro-Intestinal Stromal Tumours with positivity to the c-kit (CD117). The therapeutic basis is still today represented by surgical therapy, that must involve a complete exeresis of the tumour and needs particularly accurate operating manoeuvres, aimed at avoiding intraoperative rupture of the tumour. The recent introduction of a new drug, imatinib mesylate (STI571), has modified the therapeutic strategy and the prognosis of these tumours. The case herein presented is interesting due to the particularly large dimension of the initial tumour, the excellent response of the hepatic metastases to the imatinib mesylate therapy, the onset of a recurrence during the therapy and the accuracy of the ^{18}FDG-PET in the diagnosis of a local recurrence, which allowed a new successful operation and, finally, the initial response to the experimental therapy with Sugen (SU011248). Eur. J. Oncol., 11 (3), 193-199, 2006

Key words: **GIST, surgery, imatinib mesylate**

Riassunto

Per GIST si intende un gruppo di Tumori Stromali Gastro-Intestinali con positività per il c-kit (CD117). Il cardine terapeutico è ancor oggi rappresentato dalla terapia chirurgica, che deve prevedere un'exeresi completa del tumore e necessita di manovre operatorie particolarmente accurate, al fine di evitare la rottura intraoperatoria della neoplasia. La recente introduzione di un nuovo farmaco, l'imatinib mesilato (STI571), ha modificato la condotta terapeutica e la prognosi nei confronti di queste neoplasie. Il caso oggetto della presente disamina è interessante per le dimensioni particolarmente voluminose della neoplasia iniziale, l'eccellente risposta delle metastasi epatiche al trattamento con imatinib mesilato, l'insorgenza di una recidiva in corso di terapia, e l'accuratezza della ^{18}FDG-PET nella diagnosi di recidiva locale, che ha consentito un reintervento coronato da successo ed infine per l'iniziale risposta alla terapia sperimentale con Sugen (SU011248). Eur. J. Oncol., 11 (3), 193-199, 2006

Parole chiave: **GIST, chirurgia, imatinib mesilato**

Introduction

The acronym GIST refers to a group of Gastro-Intestinal Stromal Tumours, of stem cell origin, showing positivity to the c-kit (CD117). Such tumours arise in the gastro-intestinal tract, particularly in the stomach and small intestine. The surgical treatment must involve a complete exeresis of the tumour, extended to the contiguous organs or to the resectable metastases when necessary; the lymphadenectomy is mandatory, due to the

Received/Pervenuto 12.4.2006 - Accepted/Accettato 19.6.2006
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prevalently haematic metastasization; the surgical manoeuvres must be particularly accurate, in order to avoid the intraoperative rupture of the tumour. The recent introduction of a new drug, STI571 (imatinib mesylate), has modified the therapeutic strategy and the prognosis of these tumours. The combination of radical surgery with molecular therapy offers results previously unhoped for, with a total 5-year survival rate of more than 75%[1]. The ^{18}FDG-PET is the crucial examination in the follow-up of patients submitted to antiblastic treatment: it provides precise information on the reduction of the mass and on the trans-wall metabolic activity. The case herein presented is distinctive for several features, among which the particularly large dimension of the initial tumour, the response of hepatic metastases to the treatment with imatinib mesylate, the onset of a recurrence during therapy and the accuracy of the ^{18}FDG-PET in the diagnosis of a local recurrence, which allowed a successful operation to be carried out.

Case report

G.L., a 44-year old male patient, with remote pathological anamnesis positive to swamp fever infection and to Hepatitis A Virus (HAV), submitted in January 2002 to a duodeno-jejunal resection and double hepatic metastasectomy due to a bulky tumour, with dimensions of 25 x 12 cm, starting from the proximal jejunum, with hepatic metastases in segments III and VI (figs.1a, b).

The histologic examination showed spindle and epithelioid cells with nuclei characterized by an irregular profile. The ultrastructural examination showed ribosome-rich cytoplasm, pleomorphic mitochondria, cells with phylopodial type extensions. Immunohistochemical study showed positivity for vimentin and c-kit (fig. 1c), negativity for actin, desmin, CD34, S100. Therefore a diagnosis of jejunal GIST with hepatic metastases was considered. The post-surgical period was regular, with discharge of the patient ten days after the operation.

Six months after surgery, a CT control showed the onset of new hepatic lesions. Therefore the patient began therapy with imatinib mesylate (400 mg/*die*). After eight months of therapy (March 2003), no hepatic metastases were detected by CT, thus confirming the effectiveness of the pharmacological therapy with imatinib mesylate (fig. 2a, b).

During the maintenance therapy, in December 2004, the PET showed an area of increased metabolic activity at mesogastric level (fig. 3a), in the absence of captation at hepatic level; a further spiral CT with three-dimensional reconstruction showed an oval formation at mesogastric level with the largest diameter of 5.5 cm, localized between the upper mesenteric artery and the subrenal abdominal aorta (fig. 3b).

Therefore, the diagnosis of a recurrence of the GIST was considered; due to the apparent uniqueness of the lesion, to the absence of disease recurrence at hepatic level, to the impossibility of increasing the dosage of imatinib mesylate because of leukopoenia (swamp fever-correlated), a new operation was considered. The surgery was performed four days after the interruption of imatinib therapy in order to reduce the intraoperative haemorrhagic risk.

During the second operation, 2 neoplastic recurrences were found: a first lesion, of 6 cm, tenaciously adhering to the back of the aorta, on the upper side to the left renal vein and to the postero-inferior pancreatic vein, on the left to the gonadal vasa, on the right to the upper mesenteric vasa and to the origin of the portal vein; the second lesion, of 4 cm, was located in proximity of the duodeno-jejunal anastomosis. Peritumoural adenopaties or hepatic metastases were not detected. Therefore the exeresis of the two recurrences was performed (fig. 4).

Histological examination showed necrotic areas, spindle and epithelioid cells, mitotic activity 10/50 HPF (high power field); immunohistochemical study showed focal positivity for actin, focal and weak positivity for CD34, negativity for S100 protein and desmin and diffused positivity for CD117. The diagnosis of GIST relapse was therefore confirmed.

The post-surgical period was regular, and the patient was discharged after four days.

Six months after surgery, a CT control showed a recurrence of the disease, and, as a consequence, the dosage of imatinib mesylate was increased to 800 mg/*die*. A CT performed in October 2005 showed a peritoneal tumour with a large infiltration to the main bowels. In December 2005 the patient was admitted to the Internal Medicine Operative Unit with seriously declined clinical conditions. The patient has since been introduced to the experimental protocol with Sugen, with a progressive and clear improvement of his general conditions.

Discussion

The term GIST refers to a stromal tumour deriving from the cells of Cajal[2, 3], with positivity for c-kit (CD117)[4-6]. Such tumours originate more commonly in the stomach and the small intestine[7, 8] and they can sometimes reach, as in the present case, a huge size[1, 9-18]. The preoperative diagnosis is only presumptive: a transcutaneous biopsy is not advisable due to the risk of peritoneal dissemination[19] and only immunohistochemistry on the surgical specimen can provide certainty as to the histologic nature of the lesion[1,5,20]. The therapeutic basis is still today represented by surgical therapy, that must involve a complete exeresis of the tumour and needs particularly accurate operating manoeuvers, aimed at avoiding the intraoperative rupture of the tumour[14, 15, 17, 21, 22], cause of frequent post-surgical relapse. Patients submitted to surgery for primary GIST, M0, are disease-free after two years in 40%[23] to 60%[24, 25] of cases. The GISTs spread metastases through the blood, by the intracavitary route and by continuity to the contiguous organs[24, 26]; lymphatic spread is rare[25, 27]. The frequency of metastases is directly correlated to the dimensions of the tumour: it is 75% for GISTs of >10 cm[23, 28-31]. The incidence of synchronous metastases is 14% of the cases[32]. The 3-year survival rate for patients submitted to resection of the

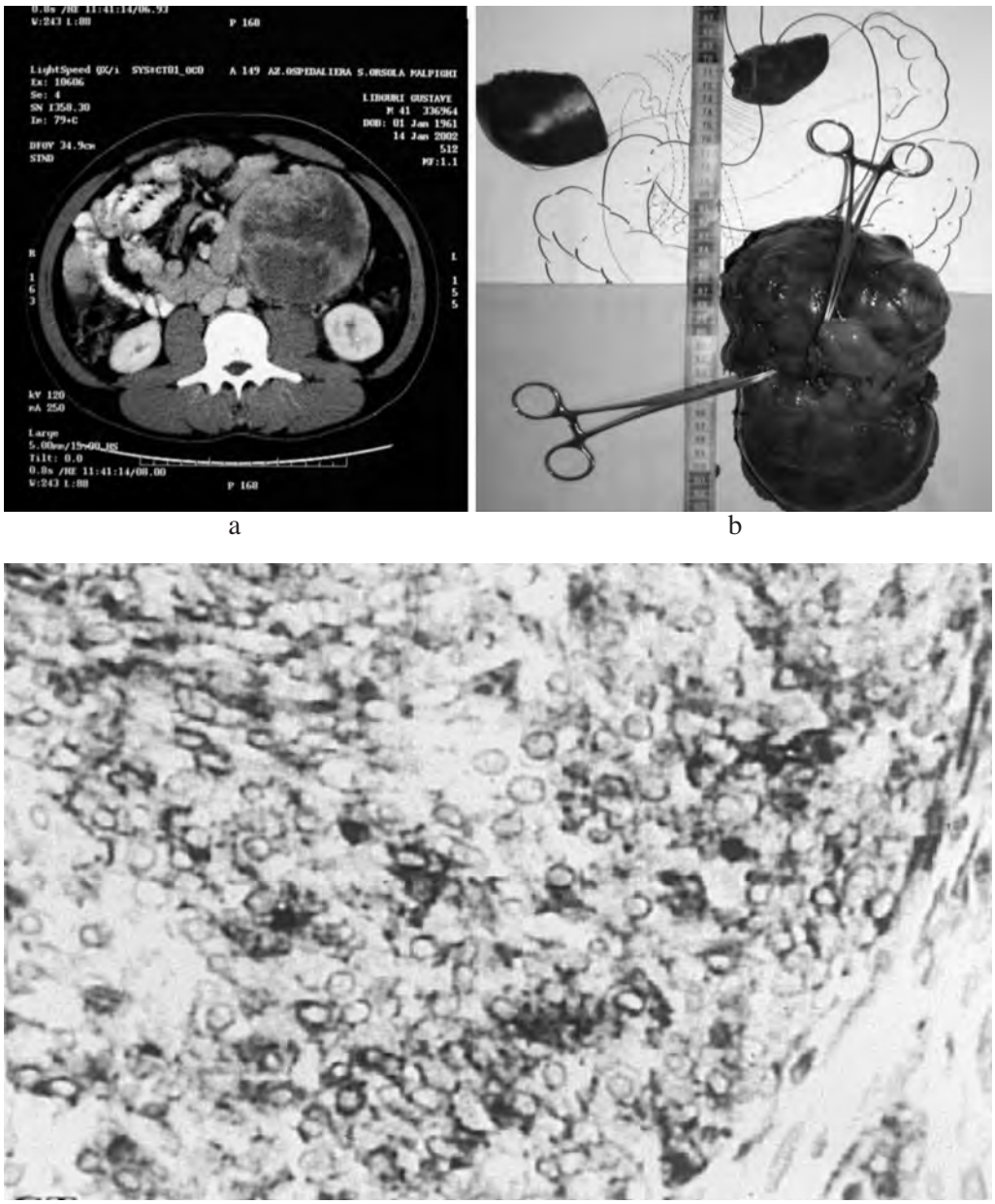
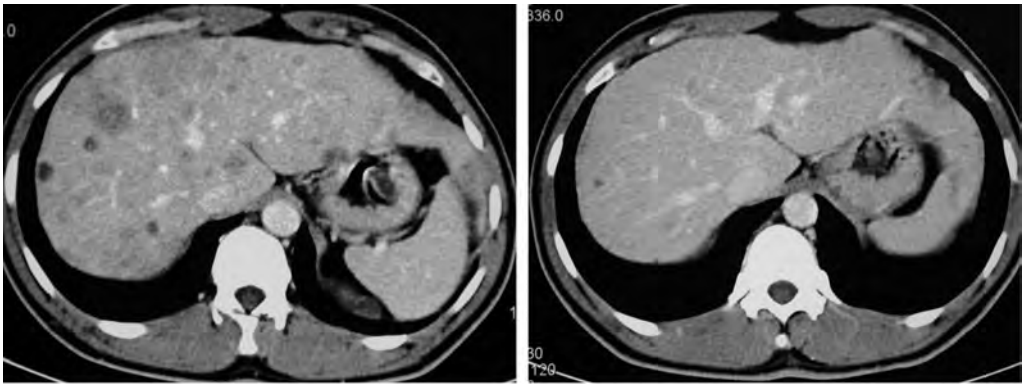


Fig. 1. a) CT image: abdominal mass with solid-cystic characteristics; metastasis in segment VI; b) surgical specimen: bulky abdominal mass with a maximum diameter of 25 cm; metastasis in hepatic segments III and VI; c) positive staining with c-kit

metastases is 58%[21], but for approximately 90% of patients who have undergone a resection, a recurrence of the disease is observed, with an average survival of 15 months[22, 33, 34]. Metachronous metastases have been reported with percentages varying from 65 to 86% of cases[21, 35]. The average time of latency between exeresis of the primitive tumour and the appearance of metastases varies from 12 to 16 months[32, 36, 37], but cases of metastases have been reported also at remarkable distance of time from the exeresis of the primitive tumour (up to 13 years according to Mosuoka *et al*[38] and Ballerini *et al*[39]; 9 years in one of our cases[26, 40]).

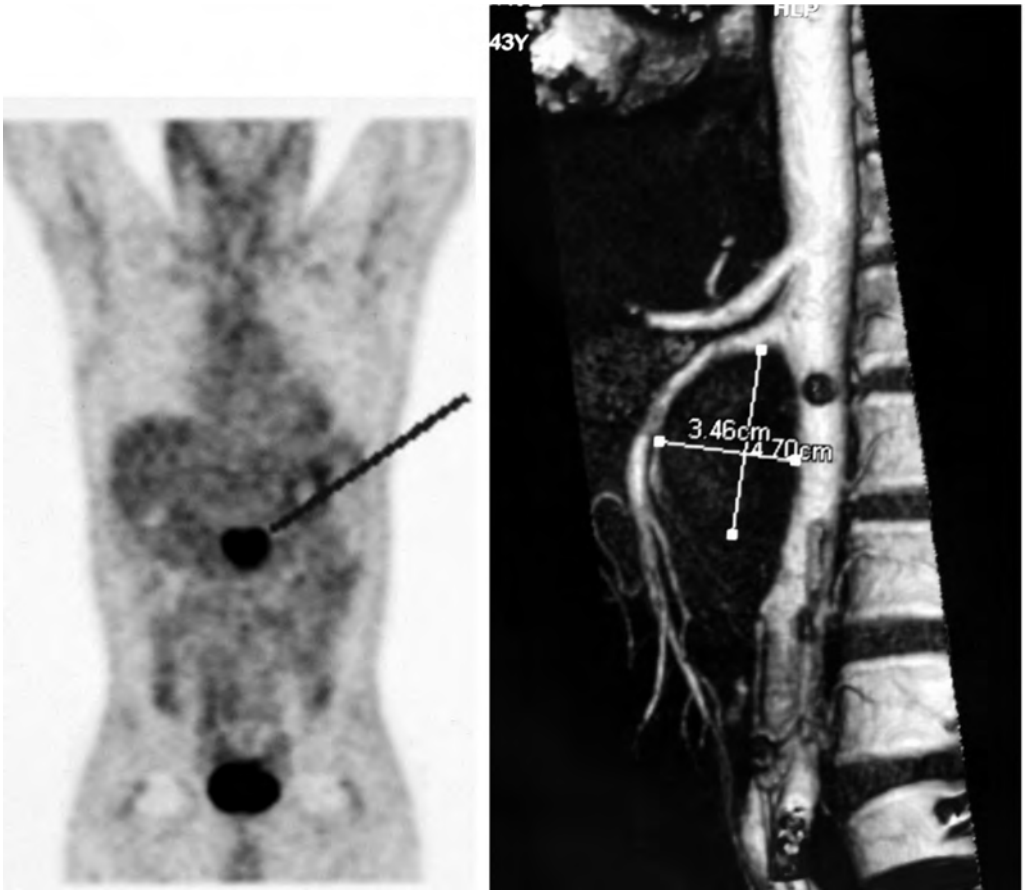
Local recurrence is frequent after complete primary resection. In the literature, a frequency of 40%[41] to 60% at 2 years from the first surgery, with an average survival of 15 months, has been reported[22, 25]. The bulky tumours, those with elevated mitotic index, and the plurifocal tumours are accompanied by a higher recurrence rate. The recurrence is characterized by an unfavourable prognosis, with a survival rate of 33% after 19 months for cases treated by surgery, or equal to 0% at 8 months for GISTs not treated by surgery[40].

With the introduction of imatinib mesylate, the prognosis of these tumours has changed. Initial results have shown partial responses in more than 50% of metastatic or locally advanced cases, opening the possibility for surgery also in patients previously judged not operable due to local diffusion or metastases[5, 42, 43]. In particular the patients showing mutation in exon 11 present a significantly better response to therapy (partial response



a b

Fig. 2. Comparison of CT controls in June 2002 (a) and March 2003 (b), showing regression of hepatic lesions



a b

Fig. 3. a) PET image: increased metabolic activity area at mesogastric level along the median line; b) spiral CT with three-dimensional reconstruction: recurrence of the GIST between the upper mesenteric artery and the abdominal aorta

rate: 78.5%) and a longer survival with respect to patients showing mutation in exon 9 (partial response rate: 45%) or tumours negative to c-kit (9% partial response rate)[44].

A study is ongoing for the use of the imatinib mesylate in neo-adjuvant or adjuvant treatment; preliminary results seem to suggest the reduction of recurrence risk in the patients with a high recurrence risk (tumours of 10 cm or more, with high mitotic index)[32].

Resistence of the tumour to pharmacologic therapy is reported in the literature and seems to be related to the onset of new mutations, in the exon 17 for GISTs with primary mutation in exon 9, and in exons 13, 14 and 17[45, 46] for GISTs with primary mutation in exon 11. The increase in the dosage (from 400 mg to 800 mg/*die*), obtained a response in some patients who were not responding to the standard dosages[47].

The ^{18}FDG-PET turns out to be useful in order to estimate the response to pharmacologic treatment and could represent a valuable prognostic tool, being able to evaluate the decreasing of the maximum standardized value of captation (SUVmax) in the first month from the beginning of therapy. The results of this examination may be particularly useful for the early diagnosis of possible

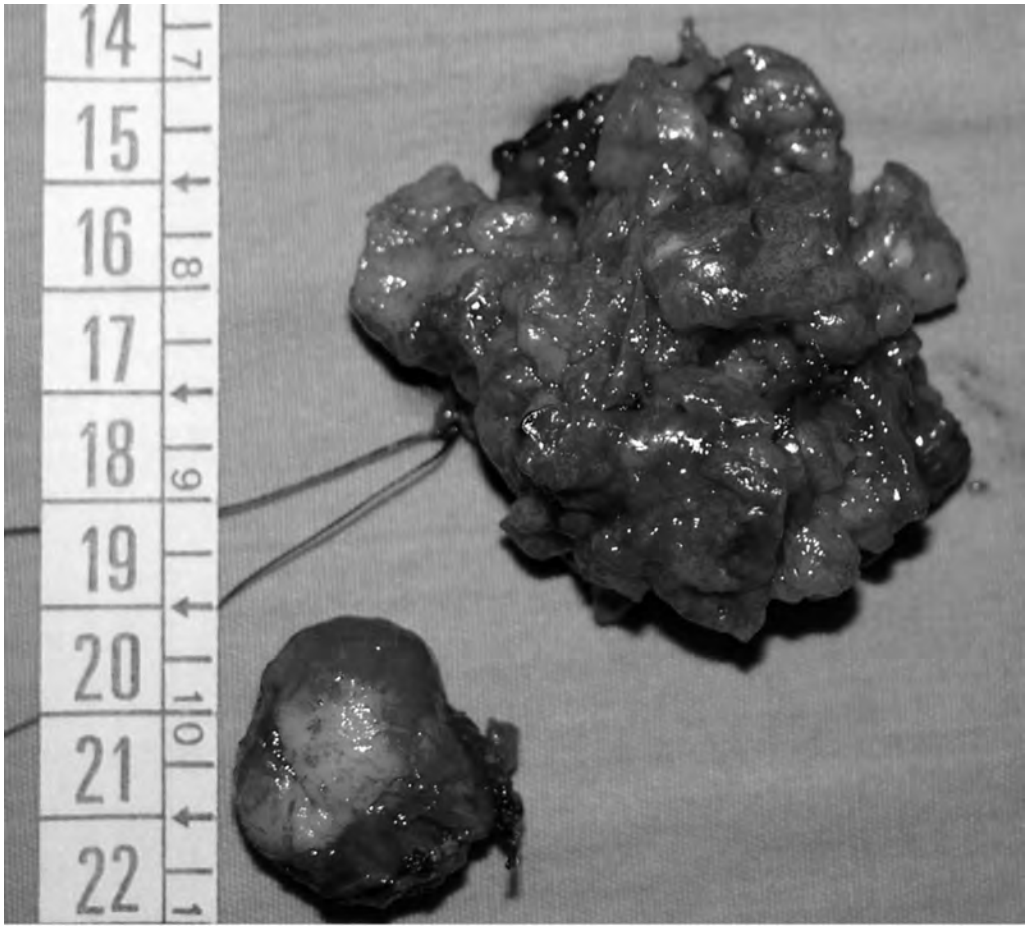


Fig. 4. Surgical specimen: recurrence of the GIST

recurrences: our hypothesis is supported by the consideration that, while PET provides information on the metabolic activity of the tumour, CT results may be useful in the topographic stadiation[48-50].

For non-responding patients, other antityrosin-kinase drugs (SU011248) are currently under study: as for STI571, they are often characterized by an antiangiogenic activity[51], act directly on the mechanisms related to tumoural growth and, from preliminary studies, seem particularly active in patients showing mutation in exon 9.

Nevertheless, in the presence of local relapses that develop in the course of treatment with imatinib mesylate, the surgical approach, when technically feasible as in the present case, seems still of fundamental importance for survival and quality of life.

Conclusions

The case herein presented is interesting and peculiar for several characteristics: the dimension of the initial lesion; the excellent response of the hepatic metastases to imatinib mesylate therapy; the onset of a local recurrence during therapy, suggesting a new mutation, the specific information from the ^{18}FDG-PET about the metabolic activity of the neoplasia, the demonstration that surgery, when technically feasible, provides favourable expectations in terms of survival and quality of life.

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Eur. J. Oncol., vol. 11, n. 3, pp. 201-203, 2006

Extrinsic obstruction of the right ureter by primary infiltrating adenocarcinoma of the gallbladder: case report

Ostruzione estrinseca dell'uretere destro per adenocarcinoma primitivo infiltrante della colecisti: caso clinico

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Summary

Primary and metastatic tumours are rare causes of ureteral obstruction. By the time diagnosis is made most of the cases are far advanced, ureteral metastasis being a manifestation of widespread systemic disease, and the prognosis is extremely poor: most of the patients die within a year. A 61-year-old woman presented with acute onset of colicky pain in the right side of her abdomen, accompanied by nausea, vomiting and fever. Abdominal computed tomography (CT) and excretory urogram (intravenous pyelogram = IVP) revealed gallbladder lithiasis with increased thickness of the gallbladder wall, right hydronephrosis and no visualization of the right ureter. Surgical exploration was performed and biopsies of the retroperitoneum were taken, cholecystectomy and right nephrectomy were performed. Histological examination showed a poorly differentiated gallbladder adenocarcinoma invading the muscular coating and periureteral adipose tissue. This case emphasizes the detection of a rare primary cancer that may metastasize to the ureter. Also of interest is the clinical presentation with renal colic as the initial manifestation of gallbladder cancer. Eur. J. Oncol., 11 (3), 201-203, 2006

Key words: **adenocarcinoma of the gallbladder, ureteral obstruction**

Riassunto

Tumori primitivi o metastatici sono rare cause di ostruzione ureterale. Frequentemente, i pazienti giungono alla diagnosi in stadio avanzato, quando già coesiste una diffusione sistemica, con prognosi estremamente sfavorevole: gran parte dei pazienti muore entro un anno. Viene presentato il caso clinico di una donna di 61 anni, presentatasi con dolore colico al fianco destro, accompagnato da nausea, vomito e febbre. La tomografia computerizzata (TC) addominale e l'urogramma escretorio (pielogramma intravenoso = PIV) hanno mostrato una colelitiasi con aumento dello spessore parietale della colecisti ed idronefrosi destra, senza visualizzazione dell'uretere omolaterale. È stata eseguita un'esplorazione chirurgica con colecistectomia, nefrectomia destra e biopsie retroperitoneali, che hanno mostrato, all'esame istologico, adenocarcinoma scarsamente differenziato della colecisti, con infiltrazione contestuale dei piani muscolari e del tessuto adiposo periureterale. Questo caso enfatizza il raro riscontro di un tumore primitivo con metastasi all'uretere. È interessante anche la presentazione clinica con colica renale come sintomo d'esordio di questo tumore della colecisti. Eur. J. Oncol., 11 (3), 201-203, 2006

Parole chiave: **adenocarcinoma della colecisti, ostruzione ureterale**

Received/Pervenuto 7.4.2006 - Accepted/Accettato 29.6.2006
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Introduction

There are several causes of ureteral obstruction (stones, inflammations, injuries and developmental abnormalities). Metastatic carcinoma of the ureter is uncommon. To our knowledge, only three cases of gallbladder carcinoma metastasizing to the ureter have been reported so far[1-2].

The authors describe a case of primary gallbladder adenocarcinoma metastasizing to the right ureter and causing hydronephrosis due to extrinsic ureteral obstruction

Case report

A sixty-one-year-old woman presented with acute onset of colicky pain on the right side of her abdomen, accompanied by nausea, vomiting and fever. Lower urinary tract symptoms were absent. Her previous medical history was negative for renal calculi or other kidney diseases.

The physical examination was essentially normal. Laboratory values were all within normal limits, including blood urea nitrogen and creatinine, and routine urinalysis. Abdominal computed tomography (CT) and excretory urogram (intravenous pyelogram = IVP) revealed gallbladder lithiasis with increased thickness of the gallbladder wall, right hydronephrosis and no visualization of the right ureter. A right retrograde pyelogram showed obstruction of the proximal ureter with some passage of the dye through the obstructed segment into the dilated renal pelvis.

Surgical exploration of the abdominal cavity was performed, revealing a large, taut gallbladder adherent to the hepatic-duodenal legament and right renal pelvis. The liver did not show any pathologic nodules on its surface, nor at the hilum. Biopsies of the retroperitoneum were taken and cholecystectomy with right nephrectomy was performed. Examination of the other abdominal organs, especially the stomach, colon and pancreas, did not show any neoformations.

Histologic examination of the kidney and the gallbladder showed a poorly differentiated gallbladder adenocarcinoma invading the muscular coating and periureteral adipose tissue (figs. 1, 2).

The patient had a normal postoperative course, with additional chemotherapy. After 10 months she died for progression of the disease with multiple metastases.

Discussion

The most common causes of ureteral obstruction include calculi, inflammation, traumas and developmental abnormalities. Primary and metastatic tumours are rarely causes of ureteral obstruction. Cohen *et al* [3] described the first case of ureteral metastasis from primary gallbladder carcinoma.

Carcinoma of the gallbladder is the fifth most common type of gastrointestinal carcinoma and accounts for about 4% of all carcinomas. Eight percent of the patients are female; the lesion is usually present in patients over sixty years of age and 90% of patients have associated cholelithiasis; 8% of the tumours are adenocarcinomas and the remainder are either indifferentiated or squamous cell carcinomas. By the time diagnosis is made, most of

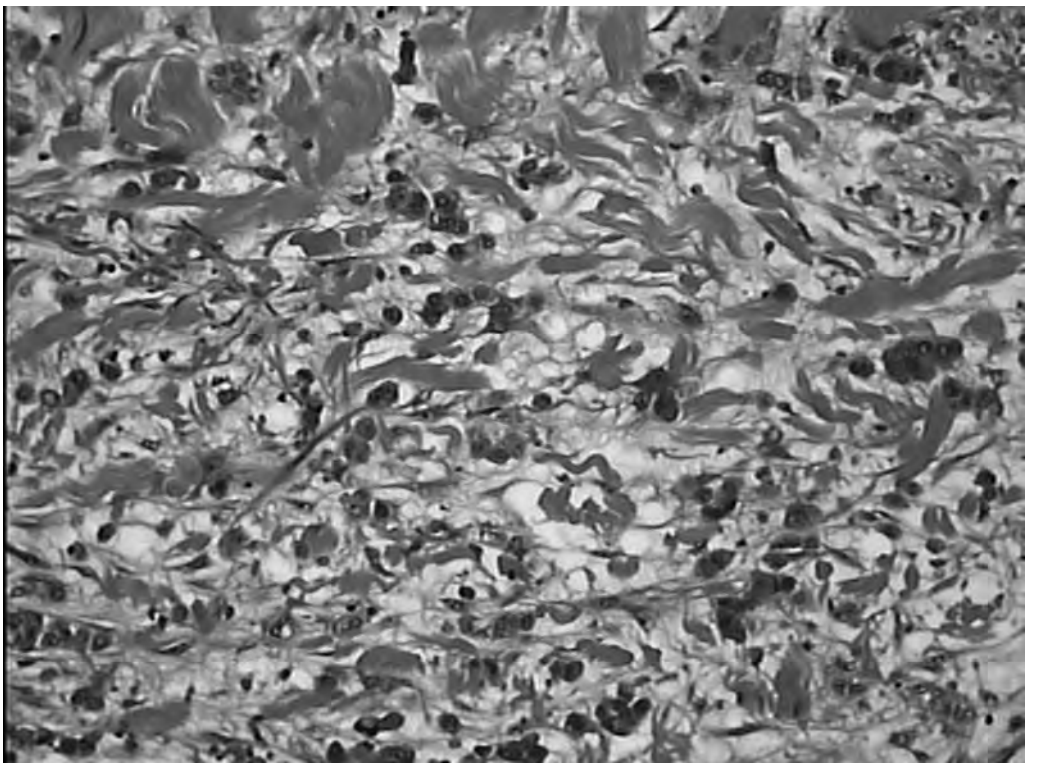

Fig. 1. Poorly differentiated gallbladder adenocarcinoma

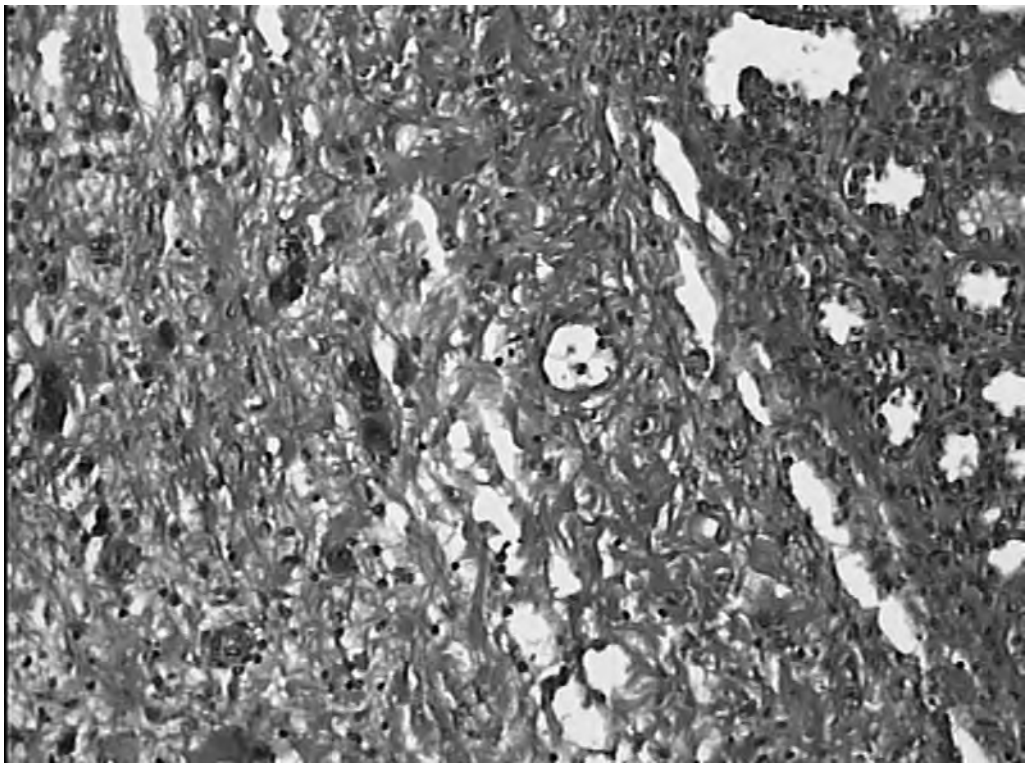

Fig. 2. Poorly differentiated gallbladder adenocarcinoma invading the muscular coating and the periureteral adipose tissue

the cases are far advanced, ureteral metastasis being a manifestation of widespread systemic disease, and most of the patients die within a year[2-4].

A correct preoperative diagnosis is made in less than 20% of cases, and in some patients cancer is found incidentally during routine cholecystectomy. Preoperative radiographic and biochemical investigations are unhelpful, but an isolated elevation in serum alkaline phosphatase level in the absence of biliary obstruction or hepatic dysfunction has been noted.

The prognosis is extremely poor. Ninety percent of patients die in one year and 50% within three months; the five-year survival rate is 1.7%[5].

In our case, except for the cholelithiasis, there were no preoperative data suggesting carcinoma of the gallbladder. The diagnosis was established by pathological examination after explorative surgery. The mechanism of ureteral obstruction was encasement and compression by a sheet of neoplastic tissue with no apparent invasion of the ureter itself[1-2].

This case emphasizes a rare primary cancer that may metastasize to the ureter. Also of interest is the clinical presentation with renal colic as the initial manifestation of gallbladder cancer. It behoves the urologist to be mindful of the protean lesions that may present with ureteral obstruction.

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Asbestos Meeting in New Delhi, 3rd December 2006

Incontro sull'Amianto a Nuova Delhi, 3 Dicembre 2006

In India, locally produced asbestos is not enough for its needs; hence much asbestos is imported from outside. Russia, Canada and Zimbabwe are the leading exporters to India. Asbestos products manufacturers have prevailed upon the government to reduce tariffs on imported material.

The efforts of the health and safety professionals, who have joined with nongovernmental organizations to create awareness about the hazards and risks of continued asbestos use, are being undermined by the industry, using its influence and propaganda that chrysotile asbestos can be safely used in a controlled manner. Industry exploits weak legislative measures and lack of data to convince policy makers that asbestos use in India has caused no health problems. There is a need to constantly apply pressure on the government and the powers that be, to realize the serious health and environmental risks associated with asbestos use.

Of an estimated 100,000 workers exposed to asbestos in India, less than 30 have been compensated. The reasons for such a small number are: refusal by management sponsored studies to grant medical certifications to workers suffering from occupational diseases, lack of training for doctors in the diagnosis of occupational lung diseases, and deliberate misdiagnosis by some doctors of asbestosis as either chronic bronchitis or tuberculosis.

In the field of occupational safety, health and the working environment, the International Labour Office (ILO) has framed 13 conventions and an equal number of recommendations so far. Of these, the Government of India has ratified 2 conventions namely the **Radiation Protection Convention (No. 115), 1960** and the **Benzene Convention (No. 136), 1971**. Some of the recent conventions, like Convention 151 of 1981 on Occupational Safety and Health and convention 161 of 1985 on Occupational Health Services, are yet to be ratified.

A recent national seminar on "Hazards of Asbestos and Silica in the Construction Industry", organized by the Director General of Factory Advice Services and Labour Institutes (DGFASLI), of the Ministry of Labour and Employment, did not invite occupational health professionals known for their work on asbestos in India or representatives of the victims' groups: this speaks volumes for the serious will to debate asbestos-related hazards in India by the authorities. In order to sensitize health professionals, environmentalists and activists, as well as the workers affected by asbestos exposure and the general population, an international meeting is going to be held in New Delhi on December 3rd, 2006. The meeting is being organized by the Maulana Azad Medical College (MAMC) along with concerned members of the civic community. It is hoped that many of our international colleagues who are seriously concerned about the continued use of asbestos would participate in the meeting and richly contribute. This would help make the task of replacing asbestos with safer substitutes a reality.

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