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The Toxic Substances Control Act Section 8(e) database: a rich source of data for studies of occupational carcinogenesis[a]

La banca dati della Legge sul Controllo delle Sostanze Tossiche (Toxic Substances Control Act) Sezione 8(e): una ricca fonte di dati per studi sulla cancerogenesi professionale

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Summary

Reports submitted to the US Environmental Protection Agency (EPA) under the authority of Section 8(e) of the Toxic Substances Control Act (TSCA) may be useful to scientists doing studies of occupational carcinogenesis. Companies are required to submit reports indicating that chemicals regulated under TSCA cause "significant risk" to human health or the environment. TSCA Section 8(e) is a unique reporting authority, in that it requires submission of positive results only, and includes unpublished data as well as results from ongoing studies. TSCA Section 8(e) reports are public documents, except for certain data which companies are permitted to claim confidential if they choose to do so. Submissions discuss results of epidemiology studies, long-term feeding studies in animals, industrial hygiene studies, chemical analyses identifying carcinogenic contaminants in products and studies of biomarkers of exposure to carcinogenic chemicals. This paper describes in some detail 8(e) submissions dealing with carcinogenesis. Eur. J. Oncol., 8 (3), 159-164, 2003

Key words: **cancer, occupational cancer, US Government, Toxic Substances Control Act**

Riassunto

I resoconti presentati all'Environmental Protection Agency degli Stati Uniti (EPA) nell'ambito della Sezione 8(e) della Legge sul Controllo delle Sostanze Tossiche (Toxic Substances Control Act - TSCA) possono essere utili per i ricercatori che si occupano di cancerogenesi professionale. Le industrie hanno l'obbligo di presentare i loro resoconti che indichino che composti chimici regolati dal TSCA comportano un "rischio significativo" per la salute dell'uomo e per l'ambiente. La Sezione 8(e) del TSCA è un organismo particolare di rendiconto, in quanto esige la presentazione dei soli risultati positivi, e comprende dati non pubblicati e risultati di studi in corso. I resoconti della Sezione 8(e) del TSCA sono documenti pubblici, con l'eccezione di alcuni dati che le compagnie, se lo vogliono, possono pretendere che siano considerati confidenziali. Tali resoconti discutono i risultati di studi epidemiologici, di studi a lungo termine su animali trattati per via alimentare, di studi di igiene industriale, di analisi chimiche per identificare i contaminanti cancerogeni nei prodotti e di studio su indici (markers) di esposizione ad agenti chimici cancerogeni. Questo lavoro descrive in dettaglio resoconti della Sezione 8(e) sulla cancerogenesi. Eur. J. Oncol., 8 (3), 159-164, 2003

Parole chiave: **cancro, tumori professionali, Governo USA, Toxic Substances Control Act**

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[a] Opinions expressed in this paper are those of the author, and should not be interpreted as representing official policy of the US Environmental Protection Agency

Introduction

The Toxic Substances Control Act (TSCA) provides statutory authority for collection and dissemination of data on toxic chemicals. Data that can be obtained under TSCA could be of great use in studies of occupational cancer. This paper focuses on information obtained under TSCA section 8(e), a unique resource for data collection and dissemination and, in particular, on submissions to EPA under TSCA Section 8(e) in 2001 and 2002.

Useful data for occupational cancer studies

Several types of data are useful for studies of occupational cancer. Of course, epidemiology studies of workplace cohorts are useful. Animal cancer bioassays can identify chemicals that may merit further examination through epidemiology, using either workplace cohort studies or case-control studies of specific cancers, with study protocols designed to assess workplace exposures.

Inhalation is most frequently the route through which hazardous chemicals enter the body in the workplace, although skin contact can be important in certain cases. Chemicals often move around in the body in a manner that makes data from studies in which the test chemical was administered by mouth (in diet or by gavage) useful as well. Exposure information is critical to evaluation of studies of occupational cancer; exposure data includes information on the identity of the chemical(s) to which workers have been exposed, which workers were exposed, how much of the chemical they were exposed to, and for how long they were exposed. Such data are important for determining cause-effect associations and for estimating the risk of developing cancer.

Product composition data, including data on product contamination with unanticipated side-products, can be used to estimate exposure to potentially carcinogenic chemicals. Mutagenicity studies, such as the Ames test (*in vitro*) or *in vivo* assays like the mouse micronucleus test, provide insights into whether chemicals interact directly with genes, or with other structures or molecules associated with cell division and/or its regulation.

Biomarkers of exposure or effect can also provide insights useful in evaluation of the rôle of chemicals in occupational cancer. Biomarkers of exposure can include DNA adducts.

All those types of data have been submitted to EPA under the authority of TSCA Section 8(e).

What is TSCA Section 8(e)?

TSCA gives the EPA authority to regulate and collect information about a very wide variety of chemicals used in industry. However, TSCA does not cover all chemicals: the law does not regulate chemicals used solely as pesticides, drugs, or food additives. If a chemical with one or more of those uses has applications as an industrial chemical as well, then that chemical is regulated under TSCA and subject to the law's requirements as regards information collection.

TSCA Section 8 is the principal reporting and information-collection section of the law. TSCA Section 8(e) is an important and unique provision under TSCA Section 8. The statutory language of TSCA Section 8(e) illustrates the importance of the provision:

"*Notice to Administrator of Substantial Risks*. Any person who manufactures, processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixtures presents a substantial risk of injury to health or the environment shall immediately inform the Administrator of such information unless such person has actual knowledge that the Administrator has been adequately informed of such information."

TSCA Section 8(e) is unique in United States laws, since it requires companies to submit to EPA all positive findings – and only positive findings – for chemicals covered under the law. The requirement that only positive findings be reported relieves government personnel of the burden of searching through company files to find positive results among what is usually a much larger number of negative studies.

There are penalties for failure to submit 8(e) reports and failure to submit reports in a timely fashion.

Companies can claim any data submitted to EPA under the authority of TSCA Section 8(e) as Confidential Business Information (CBI), but CBI status will not be afforded certain data. Specifically, health and safety data – descriptive information on studies and their results – will not be given confidential status. However, companies often claim confidentiality for the specific identity of a chemical or the chemicals in a product, and such claims of confidentiality are upheld when adequate substantiation is provided to support those claims.

The goal of TSCA Section 8(e) is to provide important information to EPA, other government agencies, and the public. Therefore, EPA serves as a steward for the 8(e) submissions, making them available to the public as quickly and efficiently as possible.

What is in the TSCA Section 8(e) data base?

Since 1978, when the TSCA Section 8(e) programme began, EPA has received over 25,000 submissions under 8(e) authority. Over 15,000 of those submissions are initial 8(e) submissions, documents in which companies (or trade associations composed of companies subject to TSCA's reporting requirements) first inform EPA of results from studies, or otherwise provide new information to the agency. There are approximately 7,500 supplemental submissions, documents that follow up on information in the initial submissions. Approximately 2,000 of the 25,000 documents submitted are FYI (For Your Information) reports, which are not required to be submitted, but are sent in by companies or others wishing to share information with EPA and, through the TSCA Section 8(e) programme, with the public. Over 10,000 of the 25,000 documents in the 8(e) programme's data base were submitted in 1991-1992 during the Compliance Audit Program (CAP), which was a sort of amnesty programme for companies that should have but had not filed 8(e) submissions during the 1980s.

TSCA 8(e) submissions on cancer

EPA receives, on average, somewhat over 300 submissions each year under the TSCA Section 8(e) programme (fig. 1). In 2001, we received 30 submissions that dealt directly with cancer (30/264 = 11% of total submissions). In 2002, we received 29

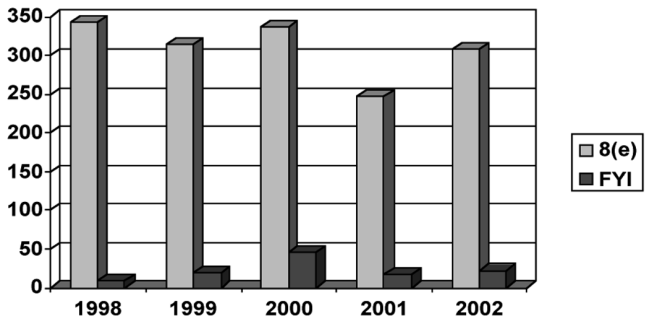

Fig. 1. Recent submissions to TSCA Section 8(e).

submissions that dealt directly with cancer (29/330 = 9% of total submissions).

An idea of the prominence of cancer studies among the submissions to EPA under the 8(e) programme can be obtained by comparing the number of cancer studies with the number of studies received for other toxicity endpoints. As would be expected, submissions dealing with acute toxicity are most prominent. Other than acute toxicity, the largest number of studies submitted in both 2001 and 2002 dealt with reproductive and developmental toxicity (Table 1). Results of studies of ecotoxicity (usually in aquatic organisms) were received almost as frequently as those dealing with reproductive and developmental toxicity.

Both epidemiology and animal studies were discussed in submissions dealing with cancer (Table 2). Two of the most important features of TSCA section 8(e) – receipt of unpublished data and data on ongoing studies – were found in several of the submissions, particularly those dealing with epidemiology studies and long-term feeding studies carried out in laboratory animals.

Although the majority of reports on animal studies stem from bioassays carried out by individual companies, several submissions each year come in from the National Toxicology Program (NTP). Typically, those submissions deal with reports from the Pathology Working Group (PWG), which reviews data from individual bioassays, and whose reports are usually influential in evaluation of bioassay results. The PWG reports complement NTP preliminary and final bioassay reports, and TSCA section 8(e) is a good source for PWG reports.

Table 1 - Toxicity endpoints in TSCA 8(e) submissions, 2001-2002

Toxicity endpoint	No. of submissions (%) of total submission in 2001	No. of submissions (%) of total submission in 2002
Reproductive or developmental toxicity	56 (21%)	64 (19%)
Ecotoxicity	33 (7.5%)	45 (14%)
Cancer	30 (11%)	29 (9%)
Mutagenicity	13 (5%)	35 (11%)

Table 2 - Types of studies represented in TSCA 8(e) submissions dealing with cancer, 2001-2002

Type of study	No. of submissions in 2001	No. of submissions in 2002
Epidemiology	3	9
Animal (not NTP)	18	16
Animal (NTP)	9	4

Examples of TSCA section 8(e) reports dealing with cancer

In this section, we review several TSCA section 8(e) reports that deal with various aspects of cancer, and could be of interest to those concerned with research in occupational cancer. The submissions selected come mostly from reports received by EPA in 2001-2002.

Epidemiology

a) In May 2002, EPA received a submission from BASF Corporation, reporting on results of a study the company had carried out of cancer incidence and mortality among workers at a plant in Geismar, LA, formerly operated by BASF[1]. The workers had been producing bentazon, an herbicide, between 1979 and 1987. An increase above expected was noted for several tumour sites. This was BASF's second 8(e) report on the production unit, with a report filed in 1997 focusing on testicular cancer cases.

b) In July 2001, Solutia Inc. sent in a TSCA 8(e) submission dealing with lymphohaemopoietic cancer mortality among workers at one of their plants[2]. According to the summary: "*The study found little evidence of increasing risk with increasing cumulative exposure for all leukemias, acute non-lymphocytic leukemias or other lymphohematopoetic cancers with the exception of multiple myeloma*".

c) A submission that came to conclusions somewhat at variance with those of Solutia as regards the carcinogenic effects of benzene was submitted by ExxonMobil in late 2001[3]. The epidemiology study covered workers employed at Australian petroleum facilities. ExxonMobil reported under TSCA section 8(e) because their Australian affiliate was one of the companies whose employees were in the study. The Australian study concluded that there was:
"Evidence for an association between previous benzene exposure in the Australian petroleum industry and an increased risk of chronic lymphocytic leukemia (CLL). This association has not been observed in previous petroleum industry benzene epidemiology studies.
An excess risk of leukemia which appears to be associated with lower cumulative exposures and exposure intensities when compared to other petroleum industry studies where an excess of leukemia risk has been found…
No evidence of an association between benzene exposure and non-Hodgkin's lymphoma or multiple myeloma was found…"

d) In March 2002, the Ethylene Oxide Industry Council of the American Chemistry Council, a trade association made up of companies that manufacture and/or market ethylene oxide, submitted information on studies on ethylene oxide carried out in Hungary[4]. The studies focussed originally on a report of a cluster of breast cancer among nurses in a hospital where ethylene oxide sterilization was in use. The sub-

mission included critiques of the Hungarian reports, including a discussion of the limitations on the unpublished study that identified the breast cancer cluster.

Products contaminated with carcinogens

a) In September 1998, BP Amoco informed EPA that : "*Chemical analysis of a polyurea-thickened grease has identified the presence of residual amounts of 4,4'-methylenedianiline (MDA) in the product. The concentration of MDA ranged from <200 ppm up to 8,200 ppm, representing a weight percent range of <0.02 to 0.82*"[5]. OSHA regulates MDA as a carcinogen, and, under the Hazard Communication standard, requires that material safety data sheets for products containing 0.1% or greater w/w of a carcinogen include information on that chemical. Therefore, BP Amoco revised its material safety data sheets accordingly, and informed purchasers of the products that were involved in what became a recall of the polyurea-thickened greases contaminated with MDA. The company that bought the grease product line from BP Amoco has stated that they use a manufacturing process that keeps the level of contamination well below 0.1% w/w. Polyurea-thickened greases are widely used and have many applications, ranging from greasing of locomotives to packing of ball bearings.

b) A submission from Cytec Industries Inc.[6], received in August 2002, discusses the identification of 2-4% ethyl carbamate as a contaminant in one of the company's products. The contaminant was identified as part of the company's efforts to determine why the product had tested positive in a mouse micronucleus test (an assay for mutagenicity). According to the company:
...Upon confirmation of the existence of ethyl carbamate in the commercial product, Cytec revised all affected MSDS with both mutagenicity and carcinogenicity warnings... The product is currently being withdrawn (or has been withdrawn in some areas) from the market and product substitution efforts are currently underway.
The Cytec submission is interesting for two reasons: it demonstrates the importance of monitoring 8(e) submissions for unexpected reports of carcinogenicity due to product contaminants, and it is an example of a submission in which a carcinogenic chemical has been shown to have mutagenic properties as well. Given the focus on mutagenicity in risk assessments for carcinogens, reports such as this can be quite important.

Chemical processes with carcinogenic side-products

a) In October 2002, EPA received TSCA 8(e) 15216[7], which was sent in by Chevron-Phillips. The company stated that: "*Chevron Phillips Chemical Company LP..... reports that it has identified a residual production of formaldehyde... in a polystyrene production unit....we are submitting this information so that it might benefit the agency and assist others who have similar processes*".
Because of the novel situation reported by Chevron Phillips, EPA provided the 8(e) submission to trade associations and labor organizations whose members might be affected by the company's information.

b) In December 2000, EPA received an 8(e) submission[8] from a company that claimed CBI for its name, location of facility, production process, and product. The 8(e) stated that the company's "*process may, under certain conditions, result in the formation of a residue of a derivative insoluble compound...The Ames screening test for mutagenicity was positive, and...the ...mouse lymphoma test also gave a positive result, suggesting the need to consider the derivative insoluble compounds as mutagenic, and a potential carcinogen*". EPA staff determined that the company's process, which used a platinum group catalyst, had features similar to those of several other processes using similar catalysts. Because of concern about exposure of production and maintenance workers at production facilities, workers who handled and transported hazardous wastes, and workers at recycling facilities where valuable catalysts were reclaimed, EPA decided to work with the company to prepare an advisory notice. The notice was prepared so as to give the public as much information as possible while preserving the CBI claims made by the company for its proprietary process. The advisory was released in 2002, with special outreach efforts to chemical industry trade associations and labor organizations. The formal advisory stands in contrast to the informal dissemination of information about the Chevron Phillips submission.

Biomarkers of exposure - human population

a) TSCA 8(e) submission 15030[9] came from the American Chemistry Council's Propylene Oxide Panel. Propylene oxide is carcinogenic in animals. The panel had previously sent EPA information on a planned, then in-progress, study of biomarkers of exposure in a workforce exposed to propylene oxide. The May 2002 submission informed the agency that "[t]he paper entitled "*Analysis of DNA and hemoglobin adducts and sister chromatid changes in a human population occupationally exposed to propylene oxide: a pilot study"* now has been published.... The published paper does not contain new information beyond that reported by the Panel in previous 8(e) submission."
The multiple endpoints assayed in the study indicate the increasing importance of molecular epidemiology. Also, in this case, illustrating 8(e)'s usefulness in tracking studies actually in progress, EPA was first informed of plans to do the study in an 8(e) submission in 1996[10], provided preliminary results as the study progressed, and finally, in the TSCA section 8(e) submission described here, given the news that the study had been published.

Biomarkers of exposure- animals

a) In October 2001, EPA received a submission from Dow Chemical[11] reporting that rats and mice exposed to 1,3-butadiene by inhalation developed DNA adducts at an exposure level of 1 ppm. That report expanded on an earlier report, received in June 2001 (14952), which reported formation of adducts at inhalation exposures of 5 ppm. Both exposure levels were considerably lower than levels at which DNA adducts had previously been reported. Dow stated in its October communication: "*As has been published previously for*

inhalation exposure to higher levels of butadiene (i.e., 20 ppm; 62.5 ppm; 200 ppm; and 625 ppm) and described in the June 8th, communication for repeated exposure to 5 ppm butadiene, detectable levels of trihydroxybutylguanine adducts were present in liver, lung and testicular tissue from the rats and mice." As of October 2001 "*[n]o written report on these results is yet available*."

This report indicates the value of 8(e) submissions, since these Dow reports are of DNA adducts being detected at much lower levels of inhaled butadiene than had been previously reported. Note also that, as of late 2001, the data had not been published, another reason the TSCA 8(e) reports should be monitored carefully.

Carcinogenicity studies in animals

a) Potassium perfluorooctanoate (PFOS) was the principal ingredient in 3M's Scotchgard products for many years. In 2000, the company ceased marketing of Scotchgard products with PFOS, and, working with EPA, withdrew from manufacturing of PFOS. There have been numerous submissions to the TSCA 8(e) programme on PFOS and its related compound, perfluorooctanoic acid (PFOA).

   In May 2001, EPA received a submission from 3M describing results of a two-year study of dietary administration of PFOS to rats[12]. The chemical was shown to cause cancer in test animals at several sites.

   Although EPA has established formal dockets for retention of submissions on PFOS and PFOA, the reports received through 8(e) are central to ongoing evaluation of the chemicals' toxicity.

b) In November 2002, EPA received a submission to TSCA section 8(e) that constituted a supplement to an initial submission[13] sent in several years earlier. That initial submission, and the subsequent supplements, deal with a "developmental pesticide," which is characterized by the submitting company as a "quinazolinone." In the November 2002 supplement, the company, whose identity is CBI, reported on follow-up pathology studies on mice fed the test chemical for 18 months. The first results of the study were submitted to EPA as 8(e) reports in January 1999, indicating, once again, the usefulness of the 8(e) programme in tracking results of in-progress studies. Tumours had been previously reported in test animals, and the November 2002 communication discussed non-neoplastic and potentially preneoplastic pathology in animals fed at levels lower than that associated with development of tumours.

   The major problem with this 8(e) submission is that the identity of the chemical has been kept CBI, so there is no way for members of the public to know precisely what the chemical is other than a "quinazolinone," which serves as a generic description, provided by the company, of the group of chemicals to which their test material belongs. The critical question is whether that description would suffice to alert individuals or organizations who might have concerns about the chemical's toxicity and who would raise those issues with EPA. Otherwise, EPA staff who have access to the confidential information serve as representatives of the public when assessing the health hazards associated with the chemical.

How to obtain information on TSCA 8(e) submissions and how to obtain the submissions themselves

There are bibliographic databases that give members of the public the opportunity to determine whether EPA has TSCA 8(e) submissions for specific chemicals and/or specific toxicity endpoints.

The on-line bibliographic databases include a substantial portion of the submissions since the 8(e) programme began in 1978, but CBI claims for chemical identity and other considerations over the years have resulted in a substantial number of submissions being omitted from the bibliographic databases.

The on-line bibliographic databases' Uniform Resource Locator (URLs) are:

– http://esc.syrres.com. That is the Website for Syracuse Research Corporation's (SRC) Toxic Substances Control Act Test Submissions (TSCATS) database. The TSCATS database tracks entries into the TSCA 8(e) system, and also contains submissions under other testing and data collection authorities of TSCA. SRC does the computer data entry for the 8(e) programme, and is likely the best bet for currency of entries. The SRC version of TSCATS can be searched for toxicity endpoints as well as individual chemicals. When companies have provided summaries or abstracts or when EPA or its contractors had prepared abstracts, those abstracts will appear when the bibliographic data appear, but the proper search/print mode must be selected to obtain the abstracts. The other two Web sources also have the abstracts available on-line.
– www.rtknet.org. RTKNet mounts the TSCATS database, using data provided by SRC on a quarterly basis.
– www.nlm.nih.gov and go to Toxnet by selecting Library Services and Databases, or go directly to Toxnet at http://toxnet.nlm.nih.gov. TSCA 8(e) entries will appear with other bibliographic references when a chemical's CAS registry number or name is entered as a search term.

Once an 8(e) report has been identified through the bibliographic data retrieval databases, one can obtain the actual report. There are three ways to obtain TSCA 8(e) reports. The best way, available only recently and for, at present, a limited part of the database, is to search the TSCA 8(e) Website online.

The TSCA 8(e) Website's URL is www.epa.gov/oppt/tsca8e. PDF versions of 8(e) reports are being produced for all incoming submissions and, as of April 2003, PDFs are available for submissions dating back to mid-2001. In time, PDF versions should be available for 8(e)s submitted before 2001.

The availability of TSCA 8(e) submissions online means that ready access to 8(e) submissions is no longer limited to individuals who can get to the EPA docket in Washington, DC. However, copies of 8(e) submissions, dating back to the initiation of the programme, can still be inspected and copied at the EPA docket, located at EPA headquarters.

TSCA 8(e) submissions can be requested through the Freedom of Information Act (FOIA). E-mail FOIA requests can be sent to hq.foia@epa.gov. Telephone requests can be made at (202) 566-1667. Mail requests can be sent to:

Freedom of Information Operations Staff Office
United States Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Mail Stop 2822T
Washington, DC 20460.

Conclusions

The TSCA section 8(e) statutory authority has afforded EPA an opportunity to establish a unique database of positive reports on toxicity, including carcinogenicity, of chemicals subject to TSCA.

This database is unlike any other in the federal government for those chemicals, and it is a good idea for those interested in occupational cancer to monitor the TSCA 8(e) submissions, utilizing the different types of submissions to guide research and medical surveillance activities.

It is likely that the most directly useful submissions to TSCA 8(e) will be those dealing directly with epidemiology studies of workforces, as well as those dealing with bioassays in animals of chemicals whose carcinogenicity has not been previously characterized, or those that describe results of monitoring for biomarkers of exposure or effect in animals or humans exposed to carcinogens. In addition, reports of product contamination or unexpected side- or byproducts of industrial processes may provide hitherto-undescribed opportunities for research or clinical activities. Finally, TSCA 8(e)s which report on results of mutagenicity tests in chemicals known to have carcinogenic effects may be of particular interest in those engaged in estimating the risk to workers of exposure to carcinogenic chemicals.

One of the most attractive features of TSCA section 8(e) for researchers and clinicians is that the programme receives results from unpublished studies, and those studies may not be available anywhere other than the company's files and TSCA section 8(e).

Limitations on availability of TSCA 8(e) reports themselves are being reduced by the recent availability of PDF versions of the reports, available online through the TSCA 8(e) Website. However, use by submitters of CBI protections to prevent disclosure of product/chemical identity can reduce the amount of data available to the public, including those with a special interest in occupational cancer.

References

Citations are to TSCA section 8(e) reports, available in PDF format on www.epa.gov/oppt/tsca8e. PDF reports are available for submissions received by the Agency after mid-2001.

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2. TSCA 8EHQ-0701-14969 (July 2001).
3. TSCA 8EHQ-0901-15006 (September 2001).
4. TSCA 8EHQ-0302-15102 (April 2002).
5. TSCA 8EHQ-0998-14258 (September 1998).
6. TSCA 8EHQ-0802-14911 (August 2002).
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9. TSCA 8EHQ-0502-15030 (May 2002).
10. TSCA 8EHQ-0796-13687 (May 1996).
11. TSCA 8EHQ-1001-15016 (October 2001).
12. TSCA FYI-0501-00373 (May 2001).
13. TSCA 8EHQ-1102-13853 (November 2002).

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Commentario/Position paper

Early detection of cancer. A new branch of oncology?

Diagnosi precoce dei tumori. Una nuova branca dell'oncologia?

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Summary

Cancer mortality has started to decrease in the Western World. The rôle played by early detection in this decrease is a matter for debate. To assess the impact on mortality it is important to distinguish between diagnosis of cancer in symptomatic patients, and early detection in asymptomatic individuals who may self-refer or who may be offered ad hoc or systematic screening. The policies for early detection and screening vary greatly between European countries, despite many similarities in their cancer burden, and this partly reflects the uncertainties surrounding asymptomatic testing for cancer. For some cancers such as those of the breast, mass screening programmes actively promoted by health authorities at a local or national level vary in their impact on cancer mortality reduction. The European School of Oncology has set up a special Task Force to address these issues, in particular the growing demand for early detection, and the first report is presented here. The task force brought together representatives from several European countries. The group recognised that combinations of early detection and screening will enforce the effectiveness of new treatments in curbing mortality curves, although policies will vary with different cancers. With the growing demand for early detection, there is a great need for cultural and scientific efforts towards structuring early detec-

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Riassunto

La mortalità per cancro ha cominciato a diminuire nel mondo occidentale. Il ruolo della diagnosi precoce in questa riduzione è oggetto di discussione. Per determinare l'impatto sulla mortalità è importante distinguere tra la diagnosi di cancro nei pazienti sintomatici e la diagnosi precoce negli individui asintomatici che si presentano spontaneamente o nell'ambito di uno screening ad hoc o sistematico. Le strategie per la diagnosi precoce e lo screening variano notevolmente nell'ambito di vari paesi europei, nonostante molte similitudini per quanto riguarda l'incidenza dei tumori, e questo riflette in parte le incertezze sugli esami per diagnosticare i tumori asintomatici. Per alcuni tumori, come quelli della mammella, l'impatto dei programmi di screening di massa, promossi dalle autorità sanitarie a livello locale o nazionale, sulla riduzione della mortalità da cancro, è variabile. La Scuola Europea di Oncologia ha istituito una speciale Task Force per affrontare questi problemi, in particolare la richiesta crescente di diagnosi precoce, e qui viene presentato il primo resoconto. La Task Force raccoglie rappresentanti di diversi paesi europei. Il gruppo ha riconosciuto che la combinazione di diagnosi precoce e screening aumenterà l'efficacia di nuovi trattamenti nell'influenzare le curve di mortalità, sebbene le strategie siano diverse per i diversi tipi di tumore. Essendoci una domanda crescente di diagnosi precoce, c'è una crescente necessità di sforzi culturali e scientifici orientati ad impostare la diagnosi precoce come competenza specifica (se non disciplina) ed a collegarla alla medicina preventiva. Per far fronte a questa domanda crescente, una soluzione potrebbe essere quella di offrire la diagnosi precoce dei tumori mediante ambulatori dedicati e non mediante ospedali, dato che l'ospeda-

tion as a specific competence (if not discipline) and linking it to preventive medicine. To cope with rising demand, one solution would be to promote early detection of cancer (EDC) preferably by specific outpatients clinics and not by hospitals, since the hospital is already related, in a psychological sense, to the concept of illness. Health professionals working in EDC should also receive specific training since the challenge facing them is not that of deciding whether a given lesion is, or is not, cancer, but rather whether or not an apparently healthy individual has cancer. The clinical approach to the healthy person who wishes to know their probability of already having cancer or the possibility of cancer developing in the future is very different from the traditional treatment-oriented attitude of oncologists. It is an approach which calls for different clinical and psychological skills. Eur. J. Oncol., 8 (3), 165-175, 2003

***Key words*: early detection, cancer, healthcare services**

le è di per sé collegato, sotto l'aspetto psicologico, al concetto di malattia. Inoltre gli operatori sanitari impegnati nella diagnosi precoce dovrebbero ricevere un addestramento specifico, dato che il problema che si trovano ad affrontare non è quello di decidere se una data lesione è cancro o no, ma se un individuo apparentemente sano ha un tumore o no. L'approccio clinico ad un individuo sano che vuol sapere quale probabilità ha di avere già un tumore o di sviluppare un tumore in futuro è molto diverso dal tradizionale atteggiamento degli oncologi orientato al trattamento. È un approccio che richiede capacità cliniche o psicologiche diverse. Eur. J. Oncol., 8 (3), 165-175, 2003

***Parole chiave*: diagnosi precoce, cancro, servizi sanitari**

Introduction

There is a growing demand – at least in the Western World – for specific services and procedures aimed at the prevention of cancer, or at the very least, ensuring early detection in order to maximise the chances of cure.

As a consequence of awareness campaigns promoted through the media by cancer charities and associations on both sides of the Atlantic, people are increasingly ready to change their lifestyle and to adopt preventive measures to avoid cancer (or at least death by cancer). The concept of "individual cancer risk assessment" has gained favour mainly as a result of the seminal work conducted by Mitchell H. Gail for breast cancer[1]. In addition other mathematical models have now even been made available on the Internet[2].

However the need people feel to "do something" to avoid cancer death is not in general met by oncology services today. It is quite common in Europe to hear of women who were told about the importance of having a mammography and then found themselves confronted with huge waiting lists impeding their access. Another major complaint is the difficulty of concentrating the examinations into one single day and location. It can prove excessively time-consuming to undergo a mammography, PAP smear, nevi check-up and ORL examination at one and the same time (as in the case of a postmenopausal woman, who smokes ten cigarettes a day and wishes to leave for a two week holiday in the sun).

Finally, who will pay for early detection of cancer (EDC) and what evidence is there that this approach has a positive cost/benefit ratio?

Our group decided to concentrate on a set of sound, feasible and well-tested recommendations to those considering setting up clinics for the early detection and prevention of cancer.

An important and similar effort was already made in 2000 by the American Cancer Society[3] and the present paper aims to accelerate the debate on this topic, particularly in Europe.

Lung cancer

Lung cancer is the most common cancer in the world today (12.3% of all new cancers). There were estimated to be 1.2 million new cases in 2000, 52% of which occurred in the developed countries. Recently lung cancer has eclipsed breast cancer as the leading cause of cancer death in women. Tobacco smoking is by far the most important cause of lung cancer. The overall 5-year survival rate for lung cancer patients is approximately 15%. This is due, in the majority of cases, to the advanced stage at which the disease is detected. However, with early diagnosis, aggressive surgical therapy, and even intervention such as laser or electrocauter therapy in selected cases, 5-year survival rates can approach 60% for early stage disease.

Early lung cancer detection

Early lung cancer (ELC), non-small-cell type, can be broadly divided into two categories: peripheral or radio-opaque, and central or radio-occult. With some overlap, the distinguishing features of peripheral and central lesions are, respectively, prevalence, 60% : 40%; histogenesis, adenocarcinoma : squamous cell carcinoma; and prognosis, worse : better. The major tools available for ELC detection are low-dose spiral CT for peripheral lesions and sputum cytology and automated cytometry as well as conventional combined with auto-fluorescence bronchoscopy for central lesions[4]. Biomarkers, using high-throughput genomic and proteomic technologies, may prove useful for both central and peripheral tumours. Biomarkers include microsatellite instability, loss of heterogeneity, and aberrant methylation[5]. These procedures are currently being tested in large clinical trials worldwide. A fundamental question centres on whether public health policy decisions on ELC screening should await the outcome in 5-10 years, or whether some procedures for ELC detection should be offered to susceptible patients even as the trials continue. Our response to this predicament is two-fold.

In many recent case-finding studies, these procedures (with the exception of biomarkers, which are still in the early validation phase) have been shown to increase the number of early-stage lung cancers detected, when compared to non-screened statistics. Hence it would seem unjust to deprive all high-risk patients of these diagnostic tools for the many years necessary before the final results of trials in progress become available, and we therefore offer this service to such patients if not participating in the trials.

Many trials of low-dose spiral CT are in progress. Our own emphasis is on the central type ELC, and the RIDTELC Lung Study aims to validate the use of induced sputum cytology, automated sputum cytometry, conventional and auto-fluorescence bronchoscopy, and the use of biomarkers, in a controlled trial of 6000 heavy smokers aged 50-74. Baseline and incidence studies are done at *t=0* and repeated at *t=36* months, with identical annual, postal monitoring for incidental respiratory symptoms. Tentative results in the treatment group following recruitment and randomization of 2000 volunteers show a lung cancer prevalence of 1.2% with a significant shift to Stage 0, Stage I and Stage II disease.

The results from another study, the Early Lung Cancer Action Project (ELCAP) were recently published[6] showing that low-dose CT can greatly improve the likelihood of detection of small non-calcified nodules and thus of lung cancer at an earlier and potentially more curable stage.

Comment

From a public health standpoint, lung cancer is unique among the leading cancers, because the underlying causal factor responsible for approximately 87% of cases is well-known and for the most part avoidable. Despite this many adults are current or recent smokers, and a significant percentage of children still take up smoking. At the time of writing, there is no organization which recommends routine screening for lung cancer among the general adult population, or for individuals who are at higher risk due to tobacco or occupational exposure.

In view of the promising results from investigations with spiral CT and other early detection tests (e.g. biological markers in the sputum), the International Task Force strongly suggests screening for lung cancer in high risk patients (e.g. age ≥50 yrs, ≥20 cigarette/die for 20 yr). A move towards routine screening would represent a fundamental change in the approach to lung cancer, and the potential benefits of early lung cancer treatment could be enormous.

Prostate cancer

Prostate cancer is now the sixth most common cancer in the world (in terms of number of new cases), and the third in men. However in the Western world it is the most common cancer. The total annual number of cases is 513,000, i.e. 9.7% of cancers in men. Prostate cancer rarely occurs before the age of 50 years; the incidence increases through the ninth decade of life. Thirty percent of men older than 50 years with no clinical evidence of prostate cancer will demonstrate a focus of cancer within the prostate at the time of autopsy.

Early detection of prostate cancer

Prostate specific antigen (PSA) was the first Food and Drug Administrations (FDA) approved tumour marker for the early detection of prostate cancer and has been employed since 1994. For screening, PSA should be used as a first line test. There are as yet no general guidelines for screening or biopsy use[7].

As one of the main points of this Task Force meeting, we conclude that at least a six-core biopsy, including a repeat biopsy within 3-6 months, should be performed if there is a risk of prostate cancer.

Within the PSA ranges 4-10 ng/ml (90 or 95% sensitivity) and also 2-4 ng/ml (90 or 95% specificity) the ratio of free to total PSA can increase the rate of detected cancers per biopsy[8]. Neural networks using PSA, free PSA and additional clinical data such as age and prostate volume are recommended to further improve the cancer detection rate. Our developed programme "ProstataClass" can further increase the specificity at given sensitivities by 20-30%[9].

Other molecular forms of PSA such as complexed PSA, alpha-2-macroglobulin PSA or alpha-1-protease-inhibitor PSA are unlikely to improve specificity over free PSA. Subforms of free PSA such as proPSA, BPSA or intact PSA are still undergoing research and have yet to be tested in large cohorts[10].

Preliminary investigations are underway into another member of the kallikrein family, human glandular kallikrein 2 (hK2), which could yield substantial additional information and prove valuable in detecting prostate cancer, especially at low PSA values. Other members of the expanded human kallikrein family may also add clinical information for early detection of prostate cancer[11]. Until now, the Gleason grade 4/5-cancer volume has been the only independent predictor of biochemical failure after radical prostatectomy. Therefore new markers indicating cancer progression are urgently needed. Current microarrays are capable of identifying genes which are overexpressed in prostate cancer. Antibody production for these related proteins may open up new ways for the development of serum markers.

Comment

The recent trend in prostate cancer incidence is characterised by a dramatic increase in incidence rates beginning in the mid-1980s and peaking in 1993. This is mostly due to the introduction of PSA testing for early prostate cancer detection. The five-year survival is nearly 100% when the disease is diagnosed at a local or regional stage, but poor when the disease is diagnosed with distant metastases (32.6%). In the light of new data arising from ongoing studies we suggest that PSA and digital rectal examination (DRE) be offered annually beginning at the age of 50 years. Men at high risk should begin testing at 45 years. From the promising preliminary results, we recommend further evaluation of the "ProstataClass" programme which may increase the specificity still more.

Cancer of the stomach

Gastric cancer, that, even in the western countries, has shown a decreasing slope in the last 50 years, is on a worldwide basis the fourth estimated tumour with 876,000 new cases, and estimated year deaths n. 647,000 during the year 2000. Almost 2/3 of the tumours occurr in the developing countries with wide variations between borderline areas.

North America is at low risk, while Japan, eastern Asia and South America are, on the contrary, highly involved.

Incidence in the male sex is anyhow twice than in females except in the younger age group.

Adenocarcinoma, with intestinal type prevailing in the high incidence countries, is the most common histologic feature; a marked increase of cancer in the cardia (related to the prevalence of Barrett's oesophagus) is observed in the same geographical areas. The high malignancy and drug-resistance of the gastric can-

cers, strongly require an adequate surveillance and possibly an aggressive potentially curative surgical approach.

Dietary risk factors and *Helicobacter pylori* infections causing atrophic gastritis are involved in the pathogenesis of gastric cancer, therefore a screening for early disease diagnosis is related to endoscopic protocols in high risk or symptomatic population[12].

Gonvers *et al* [13] suggest as definite surveillance criteria: anaemia, high grade gastric mucosa dysplasia, familial adenomatous polyposis, hereditary colorectal non polyp-born cancer and adenomas, as well as HP infection, chronic atrophic gastritis and intestinal metaplasia.

Comment

The frequency of endoscopy is reasonably stated every 2 years, but interval follow-up with less invasive methods in order to detect precancerous conditions on larger population cohorts should be relevant as a screening, thus delaying endoscopic manouvres every 3-5 years.

Balloon cytology screening for Barrett oesophagus[14] and for oesophageal cancer in general[15] has been successfully applied as a screening method in this upper GI segment.

We are now developing a simple not invasive device suitable for sample collecting fluid from the gastric cavity (Gastrotest) that might give some sort of "point of care" information about gastric physiopathology.

This very easy and scarcely invasive procedure should be applied at doctor's surgery level and even if less accurate than endoscopy because of the high patient compliance can be repeated several times in the intervals.

Colorectal cancer

Colorectal cancer comprises 13% of all cancers and is responsible for 10% of all cancer deaths. The age incidence of colorectal cancer increases steadily from the second through the eighth decades of life, with a male predominance. At diagnosis, 10% of patients have *in situ* disease, one-third have local disease, and one-third regional disease; 20% of patients have distant disease. The overall 5-year survival rate for colorectal cancer is 50%. However, when stratified by local, regional, and distant disease, the survival rates are 90%, 58%, and 5%, respectively.

Early detection of colorectal cancer

There is now solid evidence from randomized trials suggesting that it is possible to reduce mortality from colorectal cancer by 15%-25% by screening with faecal occult blood tests (FOBTs)[16]. The major benefit results from the detection of early cancer in average-risk persons above 50 years of age, who have a positive test followed by colonoscopy. However, it has to be demonstrated whether the same acceptability can be reached in the general population as that obtained in trials. Screening organizations in limited areas are needed to learn how satisfactory quality assurance can be obtained before a country-wide screening programme is set up. So far, screening has not resulted in a reduced incidence of colorectal cancer in true population studies, despite removal of two to three times as many possible precursors compared to controls. Cost-effectiveness will probably be as good as that from screening for breast cancer with mammography and better than that for cervical cancer. However, the calculations are based on the unhydrated Hemoccult-II test in randomized trials. More sensitive methods would be attractive, but none has yet been evaluated properly in average-risk persons.

The major possible alternative to FOBT is flexible sigmoidoscopy (FS). The flexiscope trial consists in evaluating a one-off FS followed by colonoscopy when high risk adenomas are detected. The aims of the trial are to test the efficacy, practicality, acceptability and safety of the process[17]. Individuals were sent hypothetical invitations to attend FS screening, and 53% responded that, in theory, they would be interested in taking part. One third of these were randomised to an intervention group. All these individuals were then sent real invitations: 71% of these actually attended screening (38% of the population in total). Interestingly, more men than women accepted the invitation to attend.

The FS trial hopes to produce positive results at the same time as the FOB pilot evaluation is published, in order that governments can make an informed choice about which (if any) colorectal cancer screening programme to implement.

The future of colorectal cancer screening would include better FOB tests with increased sensitivity, but maintaining specificity. New immunological tests are being developed, opening up the possibility of automation of testing[17-19]. DNA tests may also be developed.

Melanoma

Although melanoma is a relatively uncommon malignancy worldwide, its incidence has shown a dramatic increase (150%) since 1971. Melanoma incidence is similar in men and women and increases from the age of 10 years to the fifth decade. Approximately 1 in 123 Caucasians will develop melanoma in their lifetimes; lifetime risk is expected to be 1 in 90 by the year 2010.

Early detection of melanoma

In most countries, the incidence and mortality rates for malignant melanoma are low when compared with those of other tumours such as lung, breast and prostate cancers. Therefore the general population screening for melanoma is neither practical nor cost-effective. However, interest remains in early detection for the following reasons:

1) the incidence of melanoma starts to rise after the age of 25 years, and a higher number of deaths from melanoma occur under the age of 60 than for most other cancers;
2) the greater the depth of cancer growth (Breslow thickness) the poorer the survival, so it is believed that the sooner the cancer is detected, the greater the possibility of cure;
3) thin melanomas can be removed by simply excision using a local anaesthetic; they are thus inexpensive to treat, and have minimal effect on the quality of life.

Alternative options to general population screening have been studied. These include the following: health education to enable the general population to become aware of the early signs of melanoma, in order to have a timely diagnosis, targeted screening of high risk groups and opportunistic screening[20-24]. In the UK, a publicity campaign to promote early detection in the general population was launched, first in the West of Scotland[21] and then in seven areas of England and Scotland[22]. There was no conclusive evidence from either study that this method resulted in a reduction

in melanoma mortality. However, the initial phase of each campaign did increase the staff workload and the detection rate of thin melanomas. Clinics for pigmented lesions were set up during the campaigns to cope with the extra workload, and some hospitals still have such clinics to ensure a quick referral of lesions with a suspicion of melanoma.

Targeted screening can focus on very high risk groups such as those with a family history of the disease[23] or those with a phenotype which carries a higher risk than the average population, such as those with fair skin or a large number of nevi[24]. Methods for identifying people with specific phenotypes have been investigated[25-27]. In one study[28] the answers to a questionnaire completed by the general population were compared with a dermatologist's assessment of the same people attending a skin clinic. People tended to underestimate their level of risk factors, e.g., they would report fewer moles than the number identified by the dermatologist, so the questionnaire approach did not seem to be reliable. It was also found that knowledge of the early signs of melanoma was poor, suggesting that health education could be improved. Opportunistic screening has been studied, for example, when buses have toured different sites and people have been offered information and a skin check-up[29, 30].

To improve the early detection of melanoma, it is also important to study the reasons for diagnostic delay. This may partly occur because individuals do not recognise early signs on their skin, the general practitioner (GP) fails to recognise or diagnose the cancer, and dermatological counselling in the hospital is delayed[31-34]. Strategies are needed to improve the recognition by GPs of suspect lesions deserving diagnostic aids, to ensure swift referral of suspect lesions, and to evaluate the rôle of pigmented lesion clinics[31, 32].

Comment

As melanoma is a visible skin lesion, its diagnosis does not require invasive procedures. Moreover, removal of melanoma at an early stage cures the disease. Therefore, melanoma is potentially eradicable. Despite this apparent simplicity, the best strategy for detecting melanoma at an early curable stage is still a matter of debate. Recent studies have shown that the observation of less and less thick melanomas over time in many groups of people seems attributable to increasing awareness and spontaneous skin surveillance. Nevertheless, large-scale population screening would be costly and probably offer little advantage in terms of extra years of life. However, further efforts are needed for early detection. In fact, the absolute number of thick melanomas remains unchanged, mainly in older men. Promotion of skin surveillance should be given priority in older people as well as in known high-risk subjects.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a neoplasm with an increasing incidence worldwide[35]. Liver cancer is the fifth most prevalent human tumour and the third cause of cancer-related death in the world[35]. It is one of the few human cancers in which the main aetiological risk factors have been identified. Liver cirrhosis, mainly due to viruses (hepatitis B and C infections), constitutes the main risk factor, the 5-year cumulative incidence in these patients ranging between 15% to 20%[36]. Despite the wide implementation of surveillance programmes in Western countries, only 30% of HCC patients may receive potentially curative therapies; this figure decreases substantially when considering population-based registries[37]. Thus, HCC constitutes a major health-care problem.

Risk factors and cancer prevention

Cirrhosis is the main risk factor for HCC development, and underlies the neoplasm in 90% of cases in Western countries[36]. Amongst cirrhotics, hepatitis-B virus (HBV) and hepatitis-C virus (HCV) infection and alcohol intake are associated with the highest risk. Conversely, in Africa and Asia, where the HBV infection is acquired early in life and coincides with other oncogenic agents (i.e. aflatoxin), HCC may develop in around 40% of cases in a non-cirrhotic liver. Worldwide, the annual incidence of HCC in non-cirrhotic HBV patients is 0.4-0.6%, whereas in HBV-related cirrhotic patients it is 2%, and reaches 3-8% in HCV-related cirrhosis[36].

Cancer prevention may be attempted at three levels. Primary prevention aims at preventing exposure to the main carcinogens from initiating the carcinogenic process. This can be partially achieved with HBV vaccination programmes[38] or with health-care counselling, and also by avoiding aflatoxin contaminated food. Secondary prevention deals with disrupting of the progression from chronic hepatitis to cirrhosis. Patients with chronic hepatitis C may achieve sustained virological responses in 40-60% cases by using the combination of pegylated-interferon and rivabirin, thus preventing progression to cirrhosis. Similarly, in patients with chronic hepatitis B, lamivudine and adefovir are effective. These treatments decrease the proportion of patients developing cirrhosis, and this should reduce the incidence of HCC. Tertiary prevention refers to the prevention of HCC development when cirrhosis is established. This issue has only been assessed in two randomized controlled trials (RCTs), which included a small number of individuals and yielded contradictory results. Thus, large RCTs with the specific end-point of HCC prevention are needed[36].

Surveillance and prognosis of HCC

The prognosis of HCC patients varies according to the evolutionary stage at which the neoplasm is diagnosed[37]. Early diagnosis is feasible in surveillance programme settings, from which radical therapies can be embarked on. A proper selection of candidates for resection, liver transplantation and percutaneous treatments provides 5-yr survival rates ranging between 50% and 70%[37, 39, 40], whereas the best natural history of the disease reported 5-yr survival rates of 15-20%[41]. Therefore, it is assumed that radical therapies modify the natural course of the neoplasm, and reinforce the need for anticipating the diagnosis of early tumours.

Surveillance for HCC meets some of the standard criteria for instituting a cost-effective programme for any disease[38]. HCC occurs frequently in some populations at risk, it induces a significant morbidity and mortality, the population at risk accepts the need for screening, and physicians generally do believe that surveillance is necessary. However, the surveillance tests are imperfect, and recall procedures are not well established. Finally, although therapy is not highly effective, it is curative in some patients. Sur-

veillance is thus the only strategy to potentially decrease tumour-related mortality, since it may detect HCC at an early stage, when curative therapies can be applied. There are no RCTs comparing surveillance with nonsurveillance. Cohort studies and cost-efficiency modelling bear out the benefits in well-defined candidates, mainly Child-Pugh's A class cirrhotics, who would merit effective treatment if diagnosed with HCC. This discards advanced cirrhotics (Child-Pugh's C class) and those with severe associated conditions. Data on tumour volume doubling time give the rationale for the current recommended surveillance policy: echography and AFP determination every 6 months. Applying this policy, 40-80% of HCC detected are single lesions, but only half of them are radically treated[39].

From the available clinical data, the European Association for the Study of the Liver (EASL) advises the scheme of surveillance and recall policy presented in fig. 1[36]. This strategy provides a common guide for early detection and diagnostic confirmation of HCC. Diagnosis of HCC is based on cyto-histology, but reliable non-invasive criteria for cirrhotic patients are proposed. HCC may be certainly diagnosed by the contemporary findings of two imaging techniques showing a nodule > 2 cm with arterial hypervascularization, or by a single positive imaging technique associated with AFP> 400 ng/mL[36].

Comment

Early diagnosis of HCC has become the key factor in increasing the applicability of those curative therapies which offer the best chance for improving the life expectancy of such patients. The objective of these programmes is to reduce the disease specific mortality. Surveillance programmes for early detection of HCC should be addressed to a well-selected population at risk. Several epidemiological studies have also shown that the main risk factors for HCC are older age, male gender and cirrhosis of any aetiology, mainly related to chronic HBV or HCV infection, or alcohol, which is the most important factor. In Europe, cirrhosis underlies HCC in more than 90% of cases. According to these data, clinic-based programmes should be conducted in cirrhotic patients. Implementation of screening programmes in non-cirrhotic patients would probably not lead to a potential benefit. The restrictive criteria of age, stage of liver disease or baseline conditions that would preclude radical therapies should be assumed when early detection is organised.

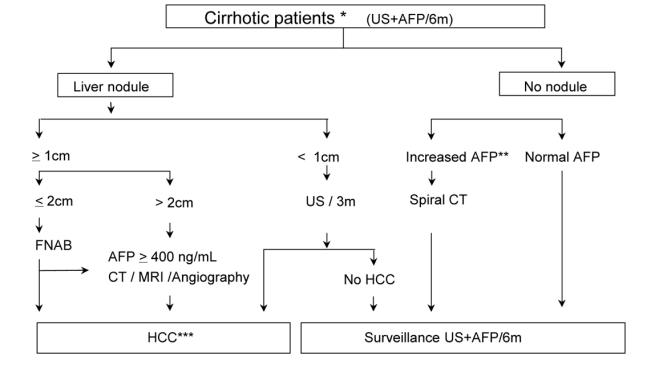

Fig. 1. Surveillance and recall strategy for HCC.

Gynaecological cancers

Gynaecological tumours affect six different sites: ovary, Fallopian tube, endometrium, cervix, vagina and vulva.

Endometrial carcinoma

Endometrial carcinoma accounts for approximately 13% of malignancies in woman and ranks fourth in frequency behind breast, lung and colon carcinomas. While endometrial carcinoma is primarily a postmenopausal disease, with a median age onset of 63 years, up to 25% of cases occur in premenopausal women, with 5% occurring in patients younger than 40 years.

Early diagnosis of endometrial cancer. Atypical genital bleeding in menopause represents an early symptom, permitting diagnosis to be made in the initial stages of the disease, with a good prognosis; no screening test will be found to decrease mortality in this clinical setting. Even in high risk groups (hormonal replacement treatment or tamoxifen users) evidence of mortality reduction from screening is lacking. Endometrial thickness as assessed by transvaginal ultrasounds allows a reduction in endometrial biopsy rate but only in symptomatic patients.

Cervical carcinoma

Cancer of the cervix uteri is the second most common cancer among women worldwide, with an estimated 468,000 new cases and 233,000 deaths in the year 2000. Almost 80% of the cases occur in developing countries where, in many regions, it is the most common cancer among women. The incidence of cervix cancer begins to rise at age 20-29 years, and the risk increases rapidly, reaching a peak usually around the age of 45-49 years in European populations.

Early diagnosis of cervical cancer. Cytological screening has demonstrated a cost-effective reduction in cancer incidence and mortality; pre-cancer detection is also achieved by periodic screening. Effective screening is mainly dependent on the system as a whole, organisation, quality control and patient communication.

The possibility of detecting and treating cancer precursors through screening intensification (annual pap-test) and combination of other cervical pre-cancer detection exams remains an open issue. There are no data on this policy, even if this practice is well accepted among gynaecologists. In this area patient information, management protocols and standard indicators are necessary but still lacking. Finally, the very high negative predictive value of HPV testing looks promising for patient reassurance.

Ovarian cancer

Carcinoma of the ovary is the fourth most common cause of death from cancer in women, accounting for 5% of all cancer-related deaths. Approximately one-quarter of all gynaecologic malignancies are of ovarian origin, and 47% of all gynaecologic can-

cer-related deaths are due to ovarian cancer. This is primarily because the disease frequently remains undiagnosed until an advanced stage.

The lifetime risk of developing ovarian cancer is approximately 1 in 70. Incidence increases with age and peaks in the eighth decade of life.

Early diagnosis of ovarian cancer is complicated by the fact that it is a disease with an unknown natural history. Occasional reports have shown a very rapid (less than three months) onset of advanced disease. Transvaginal ultrasound represents an efficacious diagnostic test, but the low specificity of the results plus the need to access the abdominal cavity as a second level investigation are factors of major concern when the test is applied in early detection and prevention settings. The use of serum marker CA125 for ovarian cancer screening is under investigation in large randomized population studies[42].

Vulvar neoplasms

They are rare and require only a careful inspection of the external genitalia by the patient or physician: information and awareness are key factors for early diagnosis.

Vaginal cancer

They are very rare neoplasms, and the pap smear generally diagnoses them as cervical cancers.

Tubal neoplasms

They are rare tumours diagnosed by ultrasound.

Comment

Most gynaecological tumours comprise cervical, endometrial and ovarian cancers; concerning prevention and early diagnosis they represent three different models (Table 1).

Since profound differences exist between evidence based screening and clinical practice, for each test it is advisable to set specific recommendations for subsequent patient management and quality standards. Patients and physicians should be fully informed on the aims, risks and benefits of undergoing testing outside evidence based screening systems.

Carcinoma of the head and neck

Approximately 67,000 cancers of the head and neck are diagnosed in the United States each year. The relative frequencies of primary head and neck tumours by site are: 40% in the oral cavity, 25% in the larynx, 15% in the oropharynx, 7% in the major salivary glands, and 13% in other sites. The male to female ratio is 3:1, and the average age at onset is approximately 50 years.

There is an increased incidence of squamous cell carcinoma (SCC) in patients with heavy tobacco and alcohol exposure.

Early detection of head and neck cancer

Head and neck tumours comprise a heterogeneous group of tumours of different origins and biological properties. However, an overwhelming proportion of these tumours are represented by skin tumours and by tumours of the mucous membrane of the oral cavity, pharynx and larynx, while tumours of salivary glands and the thyroid are rarer.

Notwithstanding their origin, all these tumours have one thing in common: their early identification is of extreme importance for the patient's outlook and survival. Tumours identified early enough permit treatment procedures that are less demanding for the patient and bring about less undesirable side effects[43, 44]. At the same time, they offer the patient a greater degree of hope for a permanent cure. However, most of these tumours are diagnosed only at an advanced stage. This is why we have been looking for ways and means to increase the percentage of patients diagnosed at an early stage.

Head and neck tumours are relatively infrequent, accounting for some 5 percent of all tumours.

Because of this low rate of incidence, head and neck tumours are not in the forefront of across-the-board preventive medical programmes. Nevertheless, patients wishing to undergo preventive medical examination to check for a potential tumour can be recommended to have an ORL examination as well.

The ear, nose and throat (ENT) examination is a relatively inexpensive, readily available and patient-friendly procedure. As most head and neck tumours are superficial formations on mu-

Table 1 - Gynaecological tumours: present status

Site	Screening (evidenced-based)	Screening under investigation	Clinical practice
Cervix	Every three years pap smear, ages 25 to 65	HPV testing to increase interval screens	Annual pap smear +/- other tests; gynaecological exam
Endometrium	No screening test	None	Transvaginal ultrasounds; gynaecological exam
Endometrium high risk (hormone replacement therapy, tamoxifen)	No screening test	Transvaginal ultrasounds; medicated IUD	Annual transvaginal ultrasounds; gynaecological exam
Ovary	No screening test	CA125	Transvaginal ultrasounds; gynaecological exam
Ovary high risk (hereditary)	No screening test	None	Genetic test; prophylactic oophorectomy in selected patients

cous membranes in the head and neck area, and because of the good accessibility of these mucous membranes for examination, it is possible to identify most of the tumours in this area at a sufficiently early stage. Consequently, the basic ENT examination is sufficient as a preventive and screening examination for head and neck tumours. As a rule, the recommended interval is 6 to 12 months.

While ENT examinations do not have a fixed place in preventive programmes focusing on the general population, regular preventive ENT examinations can definitely be recommended insofar as regards the segment of male smokers over 40, who also possibly consume increased quantities of alcohol. The population segment referred to above is in fact particularly at risk from the viewpoint of head and neck carcinomas. Unfortunately, these patients are generally less willing to take part in preventive programmes.

Although the head and neck area is one which offers relative ease of access for the purpose of examination, thus providing good prerequisites for early identification of tumours, some two-thirds of these tumours are identified at a fairly late stage. This situation is attributable to the fact that patients are late presenting themselves for examination; the tumour shows a fairly rapid progress and, at the same time, there are relatively few alarming symptoms in the early stage of the tumour ailment, which patients often mistake for feelings of discomfort associated with acute or chronic inflammations of the upper respiratory tract. In this respect, the general practitioner or dentist also play an important rôle in the early identification of tumours in addition to the obvious rôle of the otorhinolaryngologist. Every stomatological check-up includes a preventive oncological examination of the oral cavity. Similarly, every patient who suffers from hoarseness, swallowing pains or discomfort for a period in excess of three weeks and who does not respond to routine treatment should be referred by the general practitioner to a specialist: every patient visiting an otorhinolaryngologist should undergo a comprehensive ENT examination to rule out an early tumour.

In addition to the basic ENT examination focusing especially on mucous membranes, every preventive check-up should include an examination of the skin of the head and neck.

The skin is the most frequent tumour site on the human body. Most skin tumours are found in areas exposed to solar radiation, i.e. often in the head and neck area. Spinocellular and basocellular skin carcinomas are typical for groups of patients at advanced age, and these involve a relatively good outlook for the patients.

When examining the oral cavity, it is necessary to inspect all of the mucous membranes and supplement this inspection by a palpation of the tongue and the floor of the mouth. When examining the oropharynx, particular attention should be paid to the tonsils and the root of the tongue. Indirect laryngoscopy is employed to examine the tongue base and valecules. When examining the tonsils and tongue base, palpation is a very useful tool, as it often permits an early identification of an endophytic carcinoma which visual methods are capable of identifying only at the ulceration stage.

The larynx and the hypopharynx are examined by indirect laryngoscopic methods, i.e. using a mirror. In this respect, the purpose is to identify whatever changes may have occurred on the mucous membranes of the larynx and particularly in the vocal chords, to assess the freedom of movement of the vocal chords, and to determine whether the pyriform sinuses are empty and do not contain any stagnant saliva.

The nasopharynx and nasal mucous membrane examination, which is a part of the basic ENT check-up, makes use of posterior and anterior rhinoscopy. In the event of an ambiguous or pathological finding, examination of the nasal cavity and nasopharynx is supplemented by rigid rhino-epipharyngoscopy; and if considered necessary, a histological sample may be taken.

The palpation examination of the neck area should focus particularly on the lymphatic nodes, salivary glands and the thyroid gland.

It is possible to supplement the preventive ENT check-ups referred to above by a sonographic examination, which is also relatively inexpensive, available, non-invasive and patient-friendly. The examination is capable of identifying early stages of carcinomas of the salivary glands and the thyroid gland. Furthermore, sonography can also identify enlarged or borderline lymphatic nodes.

CT or MR head and neck examinations are not suitable for identifying early carcinomas and specific laboratory tests are not available.

In conclusion, an accurate clinical examination supported by ultrasound is the only tool which can reasonably be proposed in selected groups of high risk individuals to achieve an early diagnosis of head and neck tumours.

Comment

Population screening cannot be recommended for head and neck tumours in the general population, because there is inadequate understanding of the natural history and there is insufficient evidence of the utility or cost-effectiveness. A stronger case may be made for targeting screening to head and neck cancer at-risk populations, such as smokers and heavy drinkers over the age of 40 years.

Breast cancer

Breast cancer is the most frequent cancer in females and in most Western countries represents the leading cause of death in women. In Europe, 321,000 new cases were estimated in 1995[45] accounting for 17% of deaths in women. Recent data show however a decreasing trend in mortality. Since 1990, in the USA and in some European countries such as the UK, mortality rates have fallen by 1-2% per year with a corresponding increase in survival as a result of earlier detection and improved treatment. Blanks *et al* estimate that screening may exert a direct effect reducing mortality by 6.4% (range of estimates from 5.4-11.8%) compared with the effect on mortality reduction by all other factors (improved treatment with tamoxifen and chemotherapy, and earlier presentation outside the screening programme) as 14.9% (range 12.2-14.9%)[46].

There has been much debate about the value of screening mammography.

Recently Olsen and Gotzsche[47] have contested the quality of the major trials and have concluded that there is no scientific evidence that mammography screening reduces mortality.

The update overview of the Swedish randomised controlled trials on mammography screening shows a significant 21% reduction in breast cancer mortality (RR=0.79, 95% CI 0.70-0.89). The benefit in terms of cumulative breast cancer mortality started to emerge about 4 years after randomisation and continued to increase to about 10 years. The advantageous effect of breast

screening on breast cancer mortality persists after long-term follow-up[48]. The impact of screening is now under evaluation in many national and regional programmes[49]. Independent work groups of the Ministry of Health of the Netherlands, of the International Agency for Research on Cancer (IARC) in Lyon and of the European Institute of Oncology and the European School of Oncology in Milan have stated that the conclusions of Olsen and Gotzsche are not scientifically based and that there is sufficient evidence that screening mammography reduces breast cancer mortality by about 35% in women of 50-69 invited to screening.

However the potential benefit of early detection of breast cancer cannot be attributed only to mammography screening in women aged 50-69, as shown by the changes in stage distribution and by the mortality decrease in women not invited to screening at younger ages.

Moreover in younger women the sensitivity of mammography is lower and in symptomatic women the benefit of integrating mammography (Mx) with other diagnostic examinations such as physical examination (PE), ultrasounds (US) and Magnetic Resonance Imaging (MRI) is well documented. Thus a comprehensive diagnosis in specific breast units should be available for all women with early symptoms or at higher risk. Although screening procedures should be based on strict cost-effectiveness criteria, in the self-referral setting women have the right of choosing more intensive protocols such as:

– to start mammography screening at an earlier age, which has been proved to be effective in single trials[50];
– to undergo palpation and ultrasounds if they were found to have a dense parenchymal pattern which is associated with high grade cancers, i.e. both a risk factor and a reason for impaired screening sensitivity[51, 52];
– to follow a more intensive surveillance protocol if they are at high risk for hereditary cancer, although carcinogenic risks associated with radiation in these women and the benefit of early detection are not fully known[53];
– to undergo mammography examination every year if they are under Hormone Replacement Therapy (HRT), as a reduction in the sensitivity of screening mammography of between 7% and 21% in current HRT users has been observed[54] and the preclinical phase of cancers arising in these women, under oestrogen stimulation, may be shorter.

Women should be carefully informed of the potential benefits and adverse effects of these individual choices and the woman's individual risk should be assessed by means of standardised models[55].

A rough scheme of examinations that could be recommended to women in a comprehensive diagnostic breast unit, according to their age and reason for presentation could be the following (Table 2).

Comment

In conclusion we believe that early detection may significantly reduce breast cancer mortality, not only by population-based mammography screening, but also by promoting self awareness and providing high quality diagnostic services. In these units, diagnostic surveillance for each woman can be tailored according to age, risk assessment, mammographic pattern and HRT use. Dedicated and trained staff, specifically trained in risk assessment and counselling, continuous monitoring of diagnostic quality, and research activities aimed at determining the most appropriate diagnostic procedures are needed.

Early aspecific cancer detection and surveillance

One of the most puzzling and intriguing of laboratory examination for cancer screening should be aspecific markers recovered from blood during routine investigation.

Many attempts have been addressed to correlate some unbalanced serum components with preclinical or hidden cancer growth: ESR, fibrinogen, orosomucoid, fibronectin, sialomucins, cytokines, etc, have been evaluated with poor predictive rates.

Actually we are focussing on free DNA plasma concentration[56], assuming that cell necrosis or apoptotic process of malignant tumours might release measurable nuclear fragments into the blood stream. Quantitative/qualitative ratios should increase the sensitivity and specificity of this method and we strongly encourage this first line investigation followed by more specific molecular genetic details chosen on the basis of the individual risk factors. Postgenomic and proteomics[57] techniques with the microarrays method are the next future trends of early cancer detection. In fact nuclear matrix proteins are strictly related to the process of gene expression. Several extraction procedures like gel electrophoresis, matrix-surface enhanced laser desorption, ionisation with direct inspection of retained proteins by time-of flight mass spectrometry, Protein Chips and tracer free biomolecular interaction are currently used to focus the diagnosis on individual types of tumours: breast and colon, prostate and bladder can be identified at an early stage but a more general screening is expected in the near future.

Discussion

According to the authors of this report, both oncologists and health authorities will have to face an increasing demand for ear-

Table 2 - Scheme of examination for the early diagnosis of breast cancer

Age (years)	Screening	Self-referral	Very high risk (>40% life-time risk)
< 40	No screening test	PE + US in symptomatic women + Mx on request	PE and US every 6 months + MRI (?) Mx starting at 35 (?)
40-49	Screening (Mx every 12-18 months) according to Local Health Unit policy	Mx every 12-18 months + PE and US in symptomatic women	Mx every 12 months + PE and US every 6 months + MRI (?)
50-69	Mx every 24 months	Mx every 24 months (every 12 months in HRT users)+ PE and US in dense breasts(?)	Mx every 12 months + PE and US every 6 months

ly detection of cancer as a consequence of the awareness campaigns launched nearly everywhere (and certainly in Europe) by governments and cancer charities. People have now learned to cope with the idea that they can develop cancer but do not want to die from it, particularly because of delayed diagnosis: as a matter of fact the advance in genetic decodification is opening new perspectives of microarrays and proteomics techniques of cancer detection, on large population cohorts. But we have to come back to the day by day early tumours detection policy, where the state-of-the-art still leaves much to be improved in terms of evidence-based medical protocols.

In the meanwhile, preclinical research on applied genetics is supposed will supply us with very accurate weapons for prevention and diagnosis, but it will take some years of clinical investigations before that these epidemiological screenings will be part of a widespread panel of social health and welfare programming. On the other hand we do have still unresolved basic questions on this practice; for instance, who is in charge of early detection of cancer? The published data report that single Institutions (hospitals, or Universities) but also public and occupational medicine have taken the challenge for specific high risk population targets; generally speaking governments are quite reluctant to support large cancer campaigns because of the heavy cost, the very complex organization network, and the preliminary need for capillary information for the citizen.

One more question is: where can doctors and nurses "learn" early detection? We strongly believe that a formal programme in the main oncology schools, like the ESO, should be part of qualification and continuing medical education. This specific subject should enclose materials, methods and strategies for early detection in order to create in each cancer Institute or Hospital, a Registry dedicated not only to prevention but also to early diagnosis of tumours. Trained and qualified oncologists should in turn teach at CME conferences of family physicians and nurses, either to create a first step screen in their office, or to stimulate adequate follow-up and compliance of their patients with institutional trials.

The way of early detection is then open to new challenges: while waiting for definite genetic tests we ought to amplify the user network, and to improve the tools for easy and standardized screening.

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Carcinogenic and toxic effects of inhaled, non-fibrous, poorly soluble particulates in rats and mice contradict threshold lung cancer hypotheses that are dependent on chronic pulmonary inflammation

Gli effetti cancerogeni e tossici dei particolati non fibrosi e scarsamente solubili inalati da ratti e topi contraddicono le ipotesi soglia per i tumori polmonari collegate all'infiammazione polmonare cronica

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Summary

Two separate workshops, one sponsored by the International Life Sciences Institute and the other by the MAK Commission, considered the utility of rat lung tumours produced by inhaled non-fibrous poorly soluble particulates (NPSPs) for predicting human cancer risk. Based on inhalation carcinogenicity studies of diesel exhaust, carbon black, titanium dioxide, silica, and talc, the workshops concluded that the carcinogenic effects of NPSPs of low acute toxicity 1) are confined to the lungs, 2) develop only in the rat, 3) result from chronic active pulmonary inflammation and epithelial cell proliferation at particle overload doses, and 4) occur by threshold mechanisms. New insights on these issues are revealed from inhalation studies by the National Toxicology Program (NTP) of gallium arsenide, indium phosphide, molybdenum trioxide, nickel oxide, nickel subsulphide, talc, and vanadium pentoxide. Although these chemicals produced varying degrees of toxic effects in the lung of rats or mice after 14 weeks or less of inhalation exposure, the collective results of the NTP 2-year inhalation studies provide an opportunity to examine relationships between tumour outcome and non-neoplastic lesions (chronic pulmonary inflammation and alveolar epithelial hyperplasia) that have been suggested to be causally associated with lung carcinogenicity of low toxicity NPSPs. The NTP studies show that NPSPs also induce lung tumours in mice and that carcinogenic effects can occur at sites beyond the lung. Frequently in the NTP studies, lung tumour incidences were consistent with a linear or superlinear

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Riassunto

Due diversi convegni, uno sponsorizzato dall'International Life Sciences Institute e l'altro dalla Commissione MAK, hanno valutato l'utilità dei tumori polmonari prodotti nel ratto da particolati inalati non fibrosi scarsamente solubili (NPSP) nel predire il rischio di tumori nell'uomo. Sulla base di saggi di cancerogenicità per via inalatoria di emissioni di motori diesel, nerofumo, diossido di titanio, silice e talco, i convegni hanno concluso che gli effetti cancerogeni degli NPSP a bassa tossicità acuta 1) sono limitati ai polmoni, 2) si sviluppano solo nel ratto, 3) sono la conseguenza di infiammazione polmonare cronica attiva e proliferazione delle cellule epiteliali a dosi che comportano un sovraccarico di particelle, e 4) si manifestano con meccanismi soglia. Nuove informazioni su questi argomenti sono prodotte da saggi per via inalatoria condotti dal National Toxicology Program (NTP) su arsenuro di gallio, fosfuro d'indio, molibdeno triossido, nichel ossido, nichel subsolfuro, talco e vanadio pentossido. Sebbene questi composti chimici producano vari gradi di effetti tossici nei polmoni di ratti o topi dopo 14 settimane o meno di esposizione per via inalatoria, i risultati complessivi degli studi dell'NTP per via inalatoria della durata di 2 anni danno l'occasione di valutare le correlazioni fra insorgenza di tumori e lesioni non neoplastiche (infiammazione polmonare cronica ed iperplasia epiteliale alveolare), che è stato suggerito siano associate causalmente con la cancerogenicità polmonare degli NPSP. Gli studi dell'NTP mostrano che gli NPSP producono anche tumori polmonari nei topi e che gli effetti cancerogeni possono esercitarsi anche in sedi al di fuori del polmone. Spesso negli studi dell'NTP l'incidenza di tumori polmonari era compatibile con un effetto dose-risposta lineare o sopralineare e l'induzione di tumori avveniva agli attuali valori soglia ("Threshold Limit Values") o al di sotto

dose-response and tumour induction occurred at or below current Threshold Limit Values. Further, the NTP studies show that chronic pulmonary inflammation and alveolar epithelial hyperplasia are not reliable predictors of lung carcinogenicity of NPSPs. Lung tumour responses resulting from inhalation exposure to NPSPs are not readily explained by threshold-based mechanistic hypotheses. Because the carcinogenic mechanisms of NPSPs are not well understood, future research is needed to identify the multiple factors that may contribute to the carcinogenicity of these agents and to characterize those properties that account for their different dose-response relationships. Increases in lung cancer risk among workers exposed to diesel exhaust or crystalline silica dust reflect the importance of using rodent carcinogenicity data on NPSPs for the development of sound public health policies aimed at primary disease prevention. Eur. J. Oncol., 8 (3), 177-186, 2003

***Key words*: non fibrous particulates, chronic pulmonary inflammation, lung cancer, carcinogenicity bioassays**

di essi. Inoltre gli studi dell'NTP mostrano che l'infiammazione polmonare cronica e l'iperplasia epiteliale alveolare non predicono in modo sicuro la cancerogenicità degli NPSP per il polmone. L'insorgenza di tumori polmonari provocata da esposizione per via inalatoria a NPSP non si spiega facilmente con ipotesi meccanicistiche basate su valori soglia. Poiché i meccanismi della cancerogenicità degli NPSP non sono ben compresi, sono necessarie ricerche future per identificare i molteplici fattori che possono contribuire alla cancerogenicità di questi agenti e per individuare quelle proprietà che sono alla base delle diverse relazioni dose-risposta. L'aumento del rischio di tumori polmonari nei lavoratori esposti ad emissioni di motori diesel o a silice cristallina indica l'importanza di usare dati di cancerogenicità degli NPSP su roditori per lo sviluppo di valide politiche di sanità pubblica tese alla prevenzione delle malattie primitive. Eur. J. Oncol., 8 (3), 177-186, 2003

***Parole chiave*: materiali particolati non fibrosi, infiammazione polmonare cronica, tumori polmonari, saggi di cancerogenicità**

Introduction

Inhalation carcinogenic effects of non-fibrous, poorly soluble particulates (NPSPs) in laboratory animals have undergone review at two separate workshops sponsored by the International Life Sciences Institute (ILSI)[1] and by the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission)[2]. These workshops were designed to develop perspectives on mechanisms of lung tumour induction by inhaled particulates and to formulate opinions on the relevance and use of rat lung tumour data for assessing human risk. Although both workshops concluded that lung carcinogenic responses in laboratory animals exposed to NPSPs of low acute toxicity occur secondary to chronic inflammation and induction of cell proliferation, neither one defined their parameters for "low toxicity". Both reports contend that carcinogenic effects in the lung would arise only by threshold-dependent processes. More specifically, the ILSI report concludes that since "the rat model at overload is dependent on coexistent chronic inflammation and cell proliferation, at lower lung doses where chronic inflammation and cell proliferation are not present, no lung cancer hazard is anticipated".

Most particles that deposit on the bronchi are trapped in mucus and eliminated from the respiratory tract by mucociliary transport. Particles cleared from the lungs by this mechanism may be swallowed and locate in the gastrointestinal tract. In rats, approximately 10% of inhaled particles of about 1 μm in aerodynamic diameter deposit in the alveoli[3]. Particles that reach the alveoli are mostly phagocytized by alveolar macrophages, which function to transport the particles to the mucociliary escalator for clearance. Non-phagocytized particles may transfer into interstitial tissue where they may be phagocytized by interstitial macrophages and eventually accumulate in the thoracic lymph nodes.

Both the ILSI and MAK workshop reports[1, 2] endorsed the hypothesis that lung tumours induced by NPSPs of low toxicity develop as a consequence of chronic pulmonary inflammation, and that inflammation would occur only after exposures to particle concentrations that impair clearance functions of alveolar macrophages. The amount of particles in the lungs (lung burden) is at steady state when the rate of deposition of inhaled particles is equal to the rate of particle clearance. If alveolar macrophage function is impaired due to cytotoxic effects of particles or to supposed particle overload, then the rate of clearance diminishes and particles accumulate beyond their expected steady state levels. Under this circumstance, lung particle burdens increase to a disproportionately greater extent than would be expected with increasing particle exposure concentration.

Chronic pulmonary inflammation is often diagnosed in laboratory animals exposed long-term to particles of respirable size. This lesion is characterized by the accumulation of inflammatory cells (macrophages and neutrophils) in the alveolar space. Carcinogenicity of inhaled particles has been suggested to be due to reactive oxygen species (ROS) formed by inflammatory cells or by the particles themselves[2]. The increase in ROS may induce oxidative DNA damage and activate nuclear factor kB leading to increased production and release of growth promoting cytokines[4]. These growth factors are considered to be responsible for the development of hyperplasia of alveolar epithelial cells. Hyperplasia of the alveolar epithelium is an early proliferative lesion in the morphological continuum that may lead to alveolar/bronchiolar adenomas and carcinomas of the lung. The MAK Commission report[2, 5] proposes that two threshold mechanisms must be overcome for low toxicity NPSPs to induce lung tumours: 1) impairment of alveolar macrophage clearance function leading to chronic pulmonary inflammation at particle overload exposures and 2) overwhelming of antioxidant defense capacities of the lung.

Conclusions in the workshop reports were based on a small number of chemicals studied by inhalation exposure in rodents and include the following[1, 2]:

1) inhaled NPSPs of low acute toxicity induce lung tumours in rats but not in other species, including mice and hamsters; for humans a carcinogenic hazard might exist but only at ex-

posures that result in particle overload, chronic pulmonary inflammation, and increased cell proliferation;
2) carcinogenic effects of NPSPs are confined to the lungs;
3) lung tumour induction by low toxicity NPSPs requires chronic pulmonary inflammation and epithelial cell proliferation that occur only under exposure conditions in which there is impaired clearance due to excessive uptake of particles by alveolar macrophages (particle overload);
4) tumour induction occurs by a threshold mechanism (particle overload at high doses, leading to chronic inflammation and oxidative stress) and a non-linear approach would be appropriate for extrapolations of rat tumour data to humans.

These issues are re-examined in this paper with consideration to the findings from recent NTP studies of inhaled NPSPs in rats and mice.

Inhalation studies used to develop hypotheses on the carcinogenicity of NPSPs

Long-term inhalation studies on diesel exhaust particulates, carbon black, titanium dioxide, crystalline silica, and talc were instrumental in the formulation of hypotheses of ILSI and MAK on the carcinogenic effects of NPSPs. Whereas the ILSI workshop report[1] claims that human carcinogenicity data on NPSPs are consistently negative, IARC[6] and NTP[7] classify crystalline silica as a "known human carcinogen" based on sufficient evidence in humans, and diesel exhaust particulates as "probably carcinogenic to humans"[8] or "reasonably anticipated to be a human carcinogen"[7] based on elevated lung cancer rates in occupational groups exposed to diesel exhaust. Polycyclic aromatic hydrocarbons (PAHs) had been thought to be responsible for the genotoxic and carcinogenic effects of diesel exhaust particles; however, similar rat lung tumour responses with diesel exhaust and carbon black particles indicate that the carcinogenic response is not dependent on the associated organic fraction[9, 10]. Crystalline silica was considered to be different from the other NPSPs because it was thought that this toxic agent induces tumours by a mechanism involving direct generation of ROS on the particle surface causing oxidative stress, followed by an inflammatory response[2, 4].

Inhalation exposure of F344 rats to diesel exhaust at soot concentrations of 0, 0.35, 3.5, or 7.0 mg/m^3 (7 hr/day, 5 days/week for up to 30 months) produced increases in lung tumours at the two higher exposures[11]; similarly, exposure of Wistar rats to diesel exhaust at soot concentrations of 0, 0.8, 2.5, or 7.0 mg/m^3 (18 hr/day, 5 days/week for up to 24 months) produced increases in lung tumours at the two higher exposures[9]. In both studies, exposures caused increases in chronic pulmonary inflammation and alveolar epithelial cell hyperplasia. In contrast, inhalation exposure of CD-1 mice to 0, 0.35, 3.5, or 7.0 mg/m^3 (7 hr/day, 5 days/week for 24 months) or Syrian golden hamsters to 0 or 4.0 mg/m^3 (19 hr/day, 5 days/week for 27 months) did not induce lung tumours[12, 13]. Although soot particles accumulated in the lungs of mice, inflammation was not as severe as that in rats. The difference in inflammatory response was suggested as the reason why lung tumours were not increased in mice[12].

Chronic pulmonary inflammation, alveolar epithelial cell hyperplasia, and lung tumours were induced in female F344 rats and in female Wistar rats exposed by inhalation to carbon black particles for 24 months[9, 10]. Lung tumours were not induced in NMRI mice exposed to carbon black particles; however, the exposure duration in mice was only for 13.5 months[9], clearly inadequate for comparing carcinogenic effects in rats *versus* mice.

Lee *et al*[14] observed increased lung tumours in male and female Sprague-Dawley rats exposed by inhalation for 24 months (6 hr/day, 5 days/week) to 250 mg/m^3 titanium dioxide particles, but no lung tumour increase with exposure to 10 or 50 mg/m^3. In contrast, Heinrich *et al*[9] observed increased lung tumours in female Wistar rats exposed by inhalation to 7.2-12.2 mg/m^3 for 24 months (18 hr/day, 5 days/week). Male Wistar rats were not studied. The different dose-responses between these two studies may be due to smaller particle sizes (larger particle surface area) used in the Heinrich *et al* study. Heinrich *et al*[9] did not see a lung tumour response in NMRI mice exposed to titanium dioxide particles; however, the exposure duration in mice was only for 13.5 months.

The NTP conducted long-term inhalation studies of talc in F344 rats (113-122 week exposures) and B6C3F$_1$ mice (24 months exposure, 6 hr/day, 5 days/week) at concentrations of 0, 6, and 18 mg/m^3 [15]. Lung tumour rates were increased in the top dose group of female rats, yet chronic pulmonary inflammation was observed in both sexes of rats and mice at both exposure levels, and alveolar epithelial cell hyperplasia and fibrosis were increased in both sexes of rats. Adrenal gland tumours were increased in male and female rats. Lung talc burdens were not disproportionally greater in male or female rats exposed to the high concentration of talc, indicating that clearance was either impaired similarly at both exposure concentrations or that clearance was not impaired during exposure to the concentration that induced lung tumours.

Inhalation exposure of F344 rats to 1 mg/m^3 crystalline silica for 24 months (6 hr/day, 5 days/week) caused increases in chronic pulmonary inflammation, alveolar epithelial cell hyperplasia, fibrosis, and lung tumours in males and females[16]. Significantly, inhalation exposure of female Wistar rats for only one month to 0, 6, or 30 mg/m^3 followed by no exposure for up to 34 months produced increases in lung tumours at both exposure concentrations[17]. Pulmonary inflammation, but no increase in lung tumours, was seen in Balb/c mice exposed to 2 mg/m^3 crystalline silica for 19 months[18].

Although the above studies show lung tumour responses in rats but not in mice, the exposure scenarios were frequently different between species.

NTP inhalation carcinogenicity studies of NPSPs: gallium arsenide, indium phosphide, molybdenum trioxide, nickel oxide, nickel subsulphide, talc, and vanadium pentoxide

The NTP has conducted inhalation carcinogenicity studies on 9 different non-fibrous particulates; 2 of these (cobalt sulphate heptahydrate and nickel sulphate hexahydrate) are very soluble in aqueous media whereas the other 7 are poorly soluble. The NTP 2-year inhalation studies on NPSPs provide important data relevant and contradictory to mechanistic conclusions formulated by ILSI and MAK. In addition to talc, the other NTP studies on NPSPs were of nickel oxide[19, 20], nickel subsulphide[20, 21], molybdenum trioxide[22, 23], gallium arsenide[24], indium phosphide[25], and vanadium pentoxide[26, 27]. Each NPSP was studied in both sexes of F344 rats and B6C3F$_1$ mice, and except for indium phosphide, ex-

posures were 6 hr/day, 5 days/week for 2 years. Complete necropsies and histopathological examinations of all major tissues were performed on all animals. For indium phosphide, the mid and high exposure groups were stopped after 20 weeks of exposure due to increases in lung weights and severity of lung lesions (inflammation, alveolar proteinosis, and alveolar epithelial cell hyperplasia) observed at a 3-month interim evaluation[25]. Based on lung burden estimates over the course of the study, the 0.1 mg/m^3 stop-exposure group received a lower total dose of indium phosphide than the 0.03 mg/m^3 continuous exposure group.

The solubility of each chemical, the mass median aerodynamic diameter (MMAD) of particles used in these studies, and the exposure concentrations are shown in Table 1. Solubilities of these chemicals in water were less than 1 g/100 ml and in most cases less than 0.1 g/100 ml. MMADs for each of these studies were generally in the range of 1 to 2 μm; however, for talc, MMADs were approximately 2.5 to 3.5 μm. Exposure concentrations varied from 0.01 mg/m^3, the lowest exposure in the gallium arsenide study, to 100 mg/m^3, the highest exposure in the molybdenum trioxide study. For talc, exposure concentrations for the 2-year studies were based on lung burden after four weeks of inhalation exposure; for the other agents, exposure concentrations were based on toxicity after 3 months of inhalation exposure. The highest exposure levels selected for the 2-year studies reflect the relative short-term toxicities of these agents: indium phosphide > gallium arsenide ≅ nickel subsulphide > vanadium pentoxide ≅ nickel oxide >> molybdenum trioxide. Non-neoplastic lesions induced by NPSPs in the lungs of rats and mice after 13 or 14 weeks of inhalation exposure to the concentrations that were selected as the highest exposures for each 2-year study are summarized in Table 2. Indium phosphide was the only chemical in this group that caused regenerative alveolar epithelial hyperplasia after 3 months of inhalation exposure at the highest concentration used in these 2-year studies. Although each of these chemicals, except molybdenum trioxide, produced varying degrees of toxic effects in the lung of rats or mice after 14 weeks or less of inhalation exposure, the collective results of the NTP 2-year inhalation studies provide an opportunity to examine relationships between tumour outcome and non-neoplastic lesions (chronic pulmonary inflammation and alveolar epithelial hyperplasia) that have been suggested to be causally associated with lung carcinogenicity of low toxicity NPSPs.

Sites of tumour induction in rats and mice

Table 3 summarizes the sites of tumour induction in the NTP inhalation studies of NPSPs. These studies demonstrate that the lung is the most common target of tumour induction. However, the lung is not the only organ affected. Interestingly, increases in adrenal gland tumours occurred in rats exposed to 5 NPSPs: gallium arsenide, indium phosphide, nickel oxide, nickel subsulphide, and talc. In addition, mononuclear cell leukaemias were induced in female rats exposed to gallium arsenide, and liver tumours were induced in male and female mice exposed to indium phosphide. Although stress resulting from accumulation of particulates in the lungs and chronic pulmonary inflammation has been

Table 1 - Exposure concentrations used in the NTP's 2-year inhalation studies of NPSPs

Chemical/ Animal species	Solubility (g/100 ml)	MMAD[a] (μm)	Exposure concentration (mg/m^3)			
			Control	LC[b]	MC[b]	HC[b]
Gallium arsenide	<0.1					
Rats		0.8-1.0	0	0.01	0.1	1.0
Mice		0.9-1.0	0	0.1	0.5	1.0
Indium phosphide	<0.1					
Rats		1.2	0	0.03	0.1 SE[c]	0.3 SE
Mice		1.2-1.3	0	0.03	0.1 SE	0.3 SE
Molybdenum trioxide	0.5					
Rats		1.5-1.7	0	10	30	100
Mice		1.3-1.5	0	10	30	100
Nickel oxide	<0.1					
Rats		2.2	0	0.62	1.25	2.5
Mice		2.4-2.6	0	1.25	2.5	5.0
Nickel subsulphide	<0.1					
Rats		2.0-2.2	0	0.15		1.0
Mice		2.2	0	0.6		1.2
Talc	<0.1					
Rats		2.7-3.2	0	6.0		18
Mice		3.3-3.6	0	6.0		18
Vanadium pentoxide	0.8					
Rats		1.2-1.3	0	0.5	1.0	2.0
Mice		1.2-1.3	0	1.0	2.0	4.0

[a]MMAD: mass median aerodynamic diameter (mean values for each exposure chamber during the chronic studies are shown)
[b]LC: lowest concentration, MC: middle concentration, HC: highest concentration
[c]SE: stop exposure (occurred after 20 weeks in the mid and high indium phosphide exposure groups)

Table 2 - Toxic lesions of the lung in rats and mice exposed by inhalation for 13 or 14 weeks to the highest concentration of each NPSP used in the 2-year inhalation studies

Chemical/ Animal species	Exposure (mg/m^3)	Exposure-related histopathologic lesions of the lung
Gallium arsenide		
Rats	1.0	Alveolar proteinosis and histiocytic infiltration
Mice	1.0	Alveolar proteinosis, epithelial hyperplasia, and histiocytic infiltration
Indium phosphide[a]		
Rats	0.3	Diffuse chronic active inflammation (accumulation of lymphocytes, macrophages, and neutrophils), diffuse alveolar proteinosis, and regenerative alveolar epithelial hyperplasia
Mice	0.3	Chronic active inflammation, alveolar proteinosis, and regenerative alveolar epithelial hyperplasia
Molybdenum trioxide		
Rats	100	None
Mice	100	None
Nickel oxide		
Rats	2.5	Minimal chronic active inflammation in few rats
Mice	5.0	Minimal chronic active inflammation
Nickel subsulphide		
Rats	1.0	Focal chronic active inflammation (accumulation of alveolar macrophages) and focal thickening of alveolar septa
Mice	1.2	Focal chronic active inflammation (accumulation of alveolar macrophages and neutrophils) and focal alveolar fibrosis
Talc[b]		
Vanadium pentoxide		
Rats	2.0	Inflammation (accumulation of alveolar macrophages), alveolar and bronchiolar epithelial hyperplasia, and interstitial fibrosis
Mice	4.0	Multifocal inflammation (mixed cellular infiltrate) and alveolar and bronchiolar epithelial hyperplasia

[a] Effects of indium phosphide were observed after 13 weeks of the 2-year study
[b] 14-week studies were not performed with talc in rats or mice

suggested as a factor involved in the induction of pheochromocytomas of the adrenal gland, the mechanism(s) by which these agents produced adrenal gland tumours is not known. Interestingly, chronic pulmonary inflammation but not adrenal gland tumours were induced in rats exposed to gallium arsenide (males), molybdenum trioxide (males and females), and vanadium pentoxide (males and females). Thus, chronic inflammation alone is not a reliable predictor of adrenal gland carcinogenicity. The NTP studies demonstrate unequivocally that the carcinogenic effects of NPSPs are not confined to the lung.

A second important point to note in Table 3 is the induction of lung tumours in mice following inhalation exposure to indium phosphide, molybdenum trioxide, vanadium pentoxide, and possibly nickel oxide. This observation establishes that lung tumour induction from inhalation exposure to toxic NPSPs or low toxicity NPSPs is not limited to rats.

Exposure-response data for lung tumours induced by these NPSPs in rats and mice are shown in Table 4. For molybdenum trioxide and vanadium pentoxide, responses in mice were much greater than those observed in rats. These data also show that a threshold dose-response does not exist for lung tumour induction. Increases in lung tumour incidences at the lowest exposure levels for indium phosphide in rats and mice, molybdenum trioxide in mice, nickel subsulphide in rats, and vanadium pentoxide in mice

Table 3 - Sites of tumour induction in F344 rats and $B6C3F_1$ mice exposed to NPSPs by inhalation

Chemical	Male rats	Female rats	Male mice	Female mice
Gallium arsenide		Lung Adrenal gland Haematopoietic system		
Indium phosphide	Lung Adrenal gland	Lung Adrenal gland	Lung Liver	Lung Liver
Molybdenum trioxide	Lung?[a]		Lung	Lung
Nickel oxide	Lung Adrenal gland	Lung Adrenal gland		Lung?
Nickel subsulphide	Lung Adrenal gland	Lung Adrenal gland		
Talc	Adrenal gland	Lung Adrenal gland		
Vanadium pentoxide	Lung	Lung?	Lung	Lung

[a] Equivocal evidence of lung tumour induction

Table 4 - Lung tumour incidences in F344 rats and B6C3F$_1$ mice exposed to NPSPs by inhalation

Chemical/ Sex, species	Lung tumour incidence (%)			
	Control	LC[a]	MC[a]	HC[a]
Gallium arsenide				
Male rats	6	0	10	6
Female rats	0**	0	8	18**
Male mice	30	28	32	26
Female mice	14	8	8	12
Indium phosphide				
Male rats	14**	44**	60**	70**
Female rats	2**	20**	12	52**
Male mice	36	46	48	42
Female mice	8**	22*	30**	28**
Molybdenum trioxide				
Male rats	0*	2	2	8
Female rats	2	4	0	4
Male mice	22	54**	43*	36
Female mice	6**	12	16	31**
Nickel oxide				
Male rats	2	2	11	8
Female rats	2*	0	11	9
Male mice	16	21	23	20
Female mice	9	23*	19	13
Nickel subsulphide				
Male rats	0**	11*		21**
Female rats	4*	11		17*
Male mice	21*	8*		10
Female mice	16*	3*		5*
Talc				
Male rats	0	2		2
Female rats	2**	0		26**
Male mice	27	11*		23
Female mice	11	12		6
Vanadium pentoxide				
Male rats	8	20	13	18
Female rats	0	6	2	2
Male mice	44**	84**	86**	86**
Female mice	2**	64**	70**	64**

[a]LC: lowest concentration, MC: middle concentration, HC: highest concentration

* $p<0.05$, ** $p<0.01$. Asterisks in the control column indicate significance for an overall exposure-related trend; asterisks in the exposure columns indicate significance based on a pairwise comparison between the chamber controls and that exposure group

clearly establish non-threshold responses over the range of exposures used in these studies. These findings raise important occupational health concerns because the low exposure concentrations used in these studies were similar to (molybdenum trioxide and nickel subsulphide) or below (indium phosphide) the recommended Threshold Limit Values (TLV) for these agents established by American Conference of Governmental Industrial Hygienists[28].

In all of the NTP studies, except for molybdenum trioxide, lung burden measurements were taken at several time points. For these agents, lung burdens were one to three orders of magnitude less than those with talc. Except for nickel oxide in male and female rats, lung burdens increased proportionally with increasing exposure concentration. Thus, for most studies lung tumours were induced at exposures that did not appear to impair clearance functions of alveolar macrophages.

Relationships between chronic pulmonary inflammation or alveolar epithelial cell hyperplasia and lung tumour induction

The NTP studies also provide an opportunity to examine relationships between lung tumour induction by NPSPs and chronic pulmonary inflammation observed after 2 years of inhalation exposure. Data in Table 5 show that increases in lung tumour rates occur sometimes at exposure concentrations that also induce chronic pulmonary inflammation (e.g., gallium arsenide in female rats, indium phosphide in male and female rats, nickel subsulphide in male rats, talc in female rats, and vanadium pentoxide in female mice). Those findings are consistent with hypotheses that associate tumour responsiveness to NPSPs with chronic inflammation. However, there are also many instances where induction of chronic pulmonary inflammation by toxic NPSPs or low toxicity NPSPs was not associated with increased lung tumour rates (e.g., gallium arsenide in male rats, nickel oxide in male mice, nickel subsulphide in male mice, molybdenum trioxide in female rats, talc in male rats, and vanadium pentoxide in female rats). Pulmonary inflammation severity values shown in Table 5 reflect the extent of inflammatory cell accumulation (alveolar macrophages, neutrophils, and lymphocytes) within the alveoli and/or interstitium. Because criteria for severity grades differed among studies, comparisons of lesion severities are most meaningful when examined across different groups within a particular study. Even with this limitation, it is clear that for some agents the same incidence and severity of inflammation that was associated with a high incidence of lung tumours in one group (e.g., vanadium pentoxide in female mice, gallium arsenide in female rats, or talc in female rats) was not associated with a lung tumour response in a second group exposed to the same chemical (e.g., vanadium pentoxide in female rats, gallium arsenide in male rats, and talc in male rats). These data indicate that chronic inflammation induced by inhalation exposure to toxic or low toxicity NPSPs is not a reliable predictor of lung carcinogenicity.

Table 6 provides data on relationships between lung tumour induction by inhalation exposure to NPSPs and alveolar epithelial cell hyperplasia. As with chronic inflammation, there are several instances in which increases in lung tumour rates occur at exposure concentrations that also induce alveolar hyperplasia (e.g., indium phosphide in female rats, talc in female rats, vanadium pentoxide in female mice); however, there are also many examples in which lung tumour rates were increased without associated increases in alveolar epithelial cell hyperplasia (e.g., nickel oxide in rats, molybdenum trioxide in male and female mice). In addition, there are increases in alveolar epithelial cell hyperplasia that were not associated with any increases in lung tumour incidence (e.g., gallium arsenide in male rats, talc in male rats, and vanadium pentoxide in female rats). Thus, although this lesion is sometimes part of the morphological continuum leading to adenomas and carcinomas of the lung, it is not a reliable predictor of lung tumour outcome in 2-year inhalation studies.

Associations or lack of associations between lung tumour incidence and chronic pulmonary inflammation (Table 5) or alveolar

Table 5 - Relationships between chronic pulmonary inflammation and lung tumours in F344 rats and B6C3F$_1$ mice exposed to NPSPs by inhalation for 2 years

Chemical/ Sex, species	Lung lesion	Incidence % (severity[a]) Control	LC[b]	MC[b]	HC[b]
Gallium arsenide					
Male rats	Chronic inflammation	6 (1.0)	86** (1.6)	100** (2.9)	100** (3.8)
	Tumour	6	0	10	0
Female rats	Chronic inflammation	22 (1.1)	92** (1.5)	98** (2.8)	100** (3.7)
	Tumour	0	0	8	18**
Indium phosphide					
Male rats	Chronic inflammation	10 (1.2)	100** (3.8)	100** (3.4)	100** (4.0)
	Tumour	14	44**	60**	70**
Female rats	Chronic inflammation	20 (1.0)	98** (3.0)	100** (2.6)	98** (3.9)
	Tumour	2	20**	12	52**
Nickel oxide					
Male rats	Chronic inflammation	52 (1.1)	100** (1.6)	100** (2.1)	98** (2.6)
	Tumour	2	2	11	8
Male mice	Chronic inflammation	0	31** (1.6)	52** (1.4)	80** (1.4)
	Tumour	16	21	23	20
Nickel subsulfide					
Male rats	Chronic inflammation	17 (1.3)	100** (2.5)		96** (2.6)
	Tumour	0	11*		21**
Male mice	Chronic inflammation	2 (1.0)	88** (1.7)		91** (2.0)
	Tumour	21	8*		10
Molybdenum trioxide					
Female rats	Chronic inflammation	28 (1.1)	26 (1.2)	86** (1.7)	98** (3.0)
	Tumour	2	4	0	4
Talc					
Male rats	Chronic inflammation	4 (1.0)	100** (1.6)		98** (2.3)
	Tumour	0	2		2
Female rats	Chronic inflammation	4 (1.5)	98** (1.5)		100** (2.8)
	Tumour	2	0		26**
Vanadium pentoxide					
Female rats	Chronic inflammation	20 (1.5)	20 (1.1)	28 (1.2)	80** (1.7)
	Tumour	0	6	2	2
Female mice	Chronic inflammation	8 (1.0)	74** (1.3)	78** (1.8)	98** (2.0)
	Tumour	2	64**	70**	64**

[a]Severity: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[b]LC: lowest concentration, MC: middle concentration, HC: highest concentration
* $p<0.05$, ** $p<0.01$

epithelial cell hyperplasia (Table 6) do not seem to be sex or species specific. Data in Tables 5 and 6 show that while chronic inflammation may be frequently associated with alveolar hyperplasia, clear exceptions to such a relationship are also readily apparent (e.g., nickel oxide in rats).

Discussion and conclusions

Results from NTP inhalation studies on NPSPs were used to examine relationships between tumour outcome and toxic effects that have been hypothesized to be responsible for the lung carcinogenicity of low toxicity NPSPs. While we recognize that the NPSPs studied by the NTP varied in their toxicities to the lung, we believe it is appropriate to use these data to evaluate the reliability of lung lesions presumably arising from lung particle overload as predictors of lung tumour response. Of the 7 NPSPs used in this evaluation, indium phosphide was certainly the most toxic. However, the data from the indium phosphide studies were the least discriminating with respect to sorting relationships between toxic and carcinogenic effects; this is because toxic and carcinogenic responses were observed in both sexes of rats and mice exposed to this chemical. The collective information from the other NTP studies show several inconsistencies with conclusions and hypotheses developed at the ILSI and MAK workshops on the carcinogenicity of NPSPs[1, 2].

First, the NTP studies in mice demonstrate that lung tumour induction from inhalation exposure to NPSPs is not limited to rats. Lung tumours were induced in mice after inhalation exposure to indium phosphide, molybdenum trioxide, vanadium pentoxide, and possibly also nickel oxide. Particularly noteworthy is that molybdenum trioxide, which is the least acutely toxic agent among the 7 NPSPs studied by the NTP, produced a dose-related increase in lung tumours in female mice and the effects in mice were much greater than those in rats. It is possible that strain differences influence responses of mice to inhalation exposure to

Table 6 - Relationships between alveolar epithelial cell hyperplasia and lung tumours in F344 rats and B6C3F$_1$ mice exposed to NPSPs by inhalation for 2 years

Chemical/ Sex, species	Lung lesion	Incidence % (severity[a])			
		Control	LC[b]	MC[b]	HC[b]
Gallium arsenide					
Male rats	Epithelial hyperplasia	24 (2.0)	33 (1.6)	42* (2.0)	42* (2.1)
	Tumour	6	0	10	0
Indium phosphide					
Female rats	Epithelial hyperplasia	16 (1.5)	30 (2.1)	44* (2.0)	32* (1.8)
	Tumour	2	20**	12	52**
Molybdenum trioxide					
Male mice	Epithelial hyperplasia	4	2	12	4
	Tumour	22	54**	43*	36
Female mice	Epithelial hyperplasia	2	6	6	12
	Tumour	6	12	16	31**
Nickel oxide					
Male rats	Epithelial hyperplasia	0	4 (2.0)	9 (1.8)	0
	Tumour	2	2	11	8
Female rats	Epithelial hyperplasia	4 (2.0)	2 (2.0)	11 (2.5)	11 (1.5)
	Tumour	2	0	11	9
Talc					
Male rats	Epithelial hyperplasia	10 (2.0)	52** (1.3)		76** (1.7)
	Tumour	0	2		2
Female rats	Epithelial hyperplasia	4 (1.0)	56** (1.2)		94** (2.1)
	Tumour	2	0		26**
Vanadium pentoxide					
Female rats	Epithelial hyperplasia	8 (1.0)	16 (1.8)	42** (1.2)	100** (3.1)
	Tumour	0	6	2	2
Female mice	Epithelial hyperplasia	0	62** (1.6)	76** (2.0)	100** (3.3)
	Tumour	2	64**	70**	64**

[a]Severity: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[b]LC: lowest concentration, MC: middle concentration, HC: highest concentration
* $p<0.05$, ** $p<0.01$

particulates; all of the NTP studies were conducted in B6C3F$_1$ mice, while carcinogenicity studies by others on NPSPs were conducted mainly in CD-1 or NMRI mice.

Second, the NTP studies show that carcinogenic effects of these agents are not limited to the lung; tumours were also induced in the adrenal gland, liver, and haematopoietic system. The adrenal gland was the most common site of tumour induction after the lung. Because chronic pulmonary inflammation in rats was observed in several studies that did not exhibit increases in adrenal gland tumours, it would not be appropriate to conclude that in those studies in which adrenal gland tumours were increased, the tumour response was simply a consequence of stress associated with particle-induced inflammation.

Third, although threshold-based mechanistic hypotheses associated with lung particle overload have been proposed for the carcinogenic responses of inhaled NPSPs[1, 2], tumour incidence data in Table 4 demonstrate clearly a lack of threshold dose-responses for lung tumour induction. In fact, linear or superlinear dose-response curves are more consistent with the available data. Most of the NTP studies showed no evidence of lung tumour induction associated with reduced lung clearance of inhaled particles (lung particle overload), when based on proportionalities between lung burdens and exposure concentrations. Most importantly, the finding that lung tumours were induced by several of these agents at exposure levels equal to or below their recommended TLVs raises serious occupational health concerns that must not be ignored.

Fourth, while chronic pulmonary inflammation and alveolar epithelial cell hyperplasia are often associated with lung tumours after inhalation exposure to NPSPs, there are also numerous examples presented here where increases in these non-neoplastic lesions were not associated with increases in lung tumour responses in rats or mice. Hence, we conclude that increases in chronic pulmonary inflammation or alveolar epithelial cell hyperplasia are not reliable predictors of lung carcinogenicity induced by NPSPs.

Our findings reveal the pitfalls of mechanistic assertions that are based on limited or selective data. Regarding the carcinogenicity of NPSPs, the NTP inhalation studies show that responses: 1) are not confined to the lung, 2) are not rat-specific, 3) are not reliably predicted by chronic pulmonary inflammation or epithelial cell proliferation, and 4) are not readily explained by threshold-based mechanistic hypotheses.

All NPSPs studied by the NTP produced increases in lung tumour incidence in at least one sex of one species. For some chemicals, large increases in lung tumour rates were seen at low exposure concentrations, i.e. ≤ 1 mg/m^3. The reports from the ILSI and MAK sponsored workshops focussed on NPSPs that the panels

considered to be of low toxicity, though neither workshop provided an adequate definition of "low toxicity" NPSPs. Because several NPSPs studied by the NTP caused lung lesions after 2 weeks or 13 weeks of inhalation exposure, these agents might be considered to be in a different category of lung carcinogens from those addressed in the ILSI and MAK reports. However, our data show that acute toxicity is also not a reliable predictor of tumour outcome of NPSPs (e.g., tumour incidences were not increased in female rats exposed to vanadium pentoxide, male rats and male or female mice exposed to gallium arsenide, or male or female mice exposed to nickel subsulphide). We believe there is a need to ascertain whether or not the steps in the carcinogenic process are qualitatively different among NPSPs and to determine how the various pulmonary responses to these agents differ quantitatively. Grouping of some NPSPs into a category such as "low acute toxicity" is an artificial separation that has little value compared to mechanistic characterizations of those factors that contribute to the carcinogenic effects of these agents.

Carcinogenic mechanisms of NPSPs are not well understood. The particle overload/chronic inflammation hypothesis is certainly not adequate to explain the divergent data sets on NPSP carcinogenicity. Because chronic pulmonary inflammation and alveolar epithelial cell hyperplasia are not reliable predictors of tumour outcome following inhalation exposure to NPSPs, additional factors must also be involved in the carcinogenic process. Differences in particle surface area were suggested to be important for the different dose-responses for lung tumours induced by titanium dioxide particles in rats[9, 14]. In the NTP studies, MMADs were generally in the range of 1 to 2 μm. Surface reactivity and the direct generation of ROS are considered to be important factors in the carcinogenicity of crystalline silica[4]. The carcinogenicity of insoluble metal particles may be related to their uptake by phagocytosis into lung epithelial cells, partial dissolution in lysosomes, and subsequent induction of DNA damage[29]. In addition, genetic differences among different species and strains of animals, including differences in host antioxidant defence capabilities, may influence susceptibility to inflammation or tumour outcome resulting from exposure to NPSPs. Future research is certainly needed to identify the multiple factors that may contribute to the carcinogenicity of these agents and to characterize those properties that account for their different dose-response relationships. At present, there are inadequate experimental data to validate any mechanistic hypothesis on NPSP carcinogenesis.

The findings of increased lung cancer risks among workers exposed to diesel exhaust or crystalline silica dust[6-8] demonstrate that the carcinogenic effects of low toxic NPSPs and toxic NPSPs are important human health concerns. The human findings reflect the value of using rodent carcinogenicity data on NPSPs for the development of sound primary disease prevention policies. To do otherwise is not in the best interest of public health.

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Rare malignant tumours of the lung

I tumori maligni rari del polmone

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Summary

***Aims*. On the basis of a revision of their own case series the Authors discuss the various therapeutic options for primary malignant non-bronchogenic lung tumours. *Personal case series*. The Authors observed 34 cases of primary malignant lung tumours not belonging to the various histological types of bronchogenic carcinoma (0.6% of all pulmonary neoplasms observed). In 17 cases (50%) excisional surgery was performed, including 7 pneumonectomies, 4 lobectomies, 2 bilobectomies, 1 wedge resection, 1 atypical resection by thoracotomy, 1 tumourectomy by thoracotomy and 1 atypical resection by video-assisted thoracoscopic surgery (VATS); explorative thoracotomies were performed in 6 cases and the remaining 11 patients, considered inoperable, were treated by chemotherapy. Follow-up was completed in only 12 of the 17 patients operated on: 5-years survival was 33.3%. *Discussion*. The incidence of primary malignant non-bronchogenic lung tumours is very low. In agreement with the literature this paper indicates that in all histologies prognosis is directly correlated with tumour size and lymph node status at the time of diagnosis. Radical pulmonary resection with subsequent lymphadenectomy is to be considered the treatment of choice. Eur. J. Oncol., 8 (3), 187-189, 2003**

***Key words*: lung cancer, rare pulmonary neoplasms, lung surgery**

Riassunto

***Scopo*. Gli Autori, sulla base della revisione della casistica personale, riportano la terapia attuata nei tumori polmonari primitivi maligni non broncogeni. *Casistica personale*. Sono stati osservati 34 casi di tumore polmonare primitivo maligno non appartenenti alle varie forme istologiche del cancro broncogeno (0,6% di tutte le neoplasie polmonari studiate). Di essi, 17 (50%) sono stati sottoposti ad un intervento chirurgico di exeresi polmonare, che è consistito in: 7 pneumonectomie, 4 lobectomie, 2 bilobectomie, 1 wedge resection, 1 resezione atipica per toracotomia, 1 enucleazione per toracotomia ed 1 resezione atipica per chirurgia toracoscopica video-assistica (VATS); le toracotomie esplorative sono state 6 e gli altri 11 pazienti, giudicati inoperabili, sono stati indirizzati a trattamento chemioterapico. Il follow-up è stato completo soltanto in 12 dei 17 pazienti operati: la sopravvivenza a 5 anni è risultata del 33,3%. *Discussione*. I tumori polmonari maligni primitivi non broncogeni hanno un'incidenza notevolmente bassa. Con questo lavoro è stato rilevato come, in accordo con la letteratura, la prognosi sia direttamente correlata, in tutti gli istotipi, alle dimensioni del tumore e allo stato linfonodale al momento della diagnosi. L'exeresi polmonare radicale con relativa linfadenectomia è da considerarsi il trattamento di scelta. Eur. J. Oncol., 8 (3), 187-189, 2003**

***Parole chiave*: cancro del polmone, tumori rari del polmone, chirurgia polmonare**

Introduction

More than 95% of primary tumours of the lung are represented by the various histological forms of bronchogenic carcinoma; if we add carcinoids and secondary tumours, this percentage reaches approximately 99%. There are, however, other histological forms of pulmonary malignancy that are scarcely represented in the literature and have been described only in single case reports or limited case series.

Patients affected by these histological forms, which are rightly defined as "rare", are often misdiagnosed as having bronchogenic carcinoma; in fact, a definite alternative diagno-

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sis during preoperative assessment is obtained by biopsy in only 40% of cases[1-3].

The results of a review of our case series including approximately 5000 lung tumours, among which 34 rare malignancies, are presented in this paper. We discuss the clinical management and the treatment modalities adopted in these cases.

Patients and methods

The entire case series comprises 5008 patients with primary lung tumour studied at the Department of Surgery of the University of Chieti and subsequently, until December 2001, at the Fourth Department of General and Thoracic Surgery of the University of Rome "La Sapienza"; 1705 resections were performed in this series.

A diagnosis of non-bronchogenic pulmonary malignancy was made in 34 patients, 14 men and 20 women, with a median age of 47.6 years (range 11-82 years). Seventeen patients underwent pulmonary resection; in addition, 6 exploratory thoracotomies were performed, while in the remaining 11 patients, who were considered inoperable, a diagnosis was obtained by means of fine needle biopsy.

The observed histological types were classified according to the classification of lung tumours of the WHO revised in 1999[4] and are presented in Table 1.

Table 1 - Authors' case series updated until 31 December 2001

Histology	Observed cases	Resections
NSCLC	4068	1321
SCLC	357	71
Other primary malignancies	34	17
Metastases	308	116
Carcinoids	57	57
Benign tumours	184	123
Total	5008	1705

Results

The total number of patients with primary rare malignant lung tumours was 34, but only 17 cases (50%) were amenable to resection. The type of surgery relative to tumour histology is presented in Table 2. Six explorative thoracotomies were performed (17.6%), while two patients underwent palliative procedures: placement of an oesophageal endoprosthesis and laser debridement for bronchial obstruction, respectively. In 9 cases (26.5%) no invasive treatment was performed and patients received chemotherapy following diagnosis. Only one perioperative death occurred: a patient who had undergone a lobectomy for carcinosarcoma died on the 14th postoperative day. Follow-up was completed in only 12 patients (35.2%), with a median duration of 42.8 months (range 2-144 months); in this group the 5-year survival rate was 33.3%.

Discussion

In our personal experience, primary non-bronchogenic malignancies account for 0.6% of all lung tumours. These malignancies present with the same clinical features as bronchogenic carcinomas. The clinical symptoms, when present, are aspecific and mainly characterized by persistent asthenia and mild fever in the evening; in a minority of cases they are attributable to bronchial obstruction.

Transparietal or bronchoscopic biopsy techniques allow sampling of an amount of tissue that is often insufficient for the histopathological and immunohistochemical analyses required for the diagnosis of such tumours[5]. A differential diagnosis with respect to the various histological forms of bronchogenic carcinoma is therefore difficult to obtain in the period of preoperative assessment. In our experience only 14 patients (41.2%) could be diagnosed preoperatively.

In most cases the resectability of these neoplasms is slightly higher than that observed for the other histologies. The resectability rate in our case series was 50%.

Table 2 - Histological subtypes of rare malignancies among authors' case series relative to treatment

	Histology	Observed cases	Treatment[a]
Epithelial tumours	Carcinosarcoma	1	Lob
	Adenoid cystic carcinoma	6	1Pn+1Lob+1Bilob+1Wedge+ 1Endoprosth+ 1Inop
Soft tissue tumours	Haemangioendothelioma	1	1Laser debrid
	Sarcoma	3	2Inop+1Expl
	Fibrosarcoma	1	Inop
	Leiomyosarcoma	4	2Pn+2Expl
	Rhabdomyosarcoma	1	Inop
	Haemangiopericytoma	1	Atyp
	Malignant fibrous histiocytoma	4	1Pn+1Lob+1Bilob+1Expl
Lymphoproliferative disease	Hodgkin's disease	6	1Pn+1VATS+1Atyp+1Expl+2Inop
	Non-Hodgkin's lymphomas	4	1Pn+1Expl+2Inop
Germ cell tumours	Teratocarcinoma	1	Pn
Miscellaneous	Melanoma	1	Lob

[a] Pn = pneumonectomy; Lob = lobectomy; Bilob = bilobectomy; Atyp = atypical resection; VATS = atypical resection by VATS; Laser debrid = laser debridement; Endoprosth = oesophageal endoprosthesis; Expl, exploratory thoracotomy; Inop, inoperable

These rare pulmonary malignancies generally show a highly aggressive biological behaviour, with the exception of low-grade non-Hodgkin's lymphomas (small B-cell lymphoma, plasmacytoid lymphoma), in which complete remission can be obtained by combined treatment with surgery and chemotherapy. In all other histological subtypes, prognosis is directly correlated with tumour stage at the time of diagnosis. Regnard *et al* [6] reported a five-year survival rate of 83% in patients operated on for stage Ib primary lung sarcoma and 30% in stage IIb disease.

The most important negative prognostic factors common to all histological subtypes of rare lung malignancies are tumour size and lymph node status. Radical lung resection along with lymphadenectomy is therefore considered the treatment of choice. Neoadjuvant chemotherapy is generally ineffective in tumour downstaging but may be indicated for patients evaluated as inoperable. Inoperability is obviously an indication for all invasive palliative techniques (oesophageal endoprosthesis, laser debridement, etc.) that may help to improve the quality of life of these patients.

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La radioterapia adiuvante nel carcinoma mammario: timing e ruolo della IORT

Adjuvant radiotherapy of breast cancer: timing and rôle of IORT

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Riassunto

La radioterapia adiuvante dopo chirurgia conservativa sulla mammella nella sua modalità di erogazione standard è oggetto di discussione da parte di più Autori. Basandosi sul razionale che la maggior parte delle riprese di malattia avvengono nel quadrante sede del tumore originario, molti studi sono stati fatti ed altri sono in atto tuttora per valutare l'efficacia di irradiazioni parziali della ghiandola mammaria, utilizzando brachiterapia interstiziale o fasci esterni di elettroni o fotoni anche con tecniche sofisticate (radioterapia 3-D conformazionale o IMRT). Presso l'Istituto Europeo di Oncologia (IEO) è stato deciso di utilizzare la radioterapia intraoperatoria (IORT) ed è stato installato in una sala operatoria un acceleratore mobile, miniaturizzato, che eroga fasci di elettroni direttamente sulla ghiandola mammaria residua durante l'atto chirurgico. L'esperienza dell'IEO si è concretizzata attraverso uno studio di fase I (dose escalation) e uno studio di fase II (per valutare la tossicità acuta e intermedia); infine è stato varato uno studio, in corso a tutt'oggi, di fase III, per comparare l'efficacia dell'irradiazione parziale con IORT rispetto alla radioterapia convenzionale su tutta la mammella. La tossicità finora rilevata è assolutamente accettabile, ma è necessario attendere la conclusione dello studio per avere i dati preliminari, ed un adeguato follow-up per la valutazione dei risultati. Eur. J. Oncol., 8 (3), 191-193, 2003

***Parole chiave*: radioterapia adiuvante, radioterapia intraoperatoria, carcinoma mammario**

Summary

Adjuvant radiotherapy as a standard procedure after conservative surgery on the breast is a subject of discussion by many authors. Based on the radionale that most disease recurrences are observed in the quadrant of the primary tumour, many studies have been conducted and others are still ongoing to evaluate the efficacy of a partial irradiation of the mammary gland with the use of interstitial brachytherapy or external beams of electrons or photons, also with sophisticated techniques (conformational 3-D radiotherapy or IMRT). At the European Institute of Oncology (EIO), it has been decided to use intraoperative radiotherapy (IORT), and a mobile, miniaturized accelerator, delivering electron beams directly on the residual mammary gland during surgery, has been set up in an operating room. The experience of the EIO has been drawn from a phase I study (dose escalation) and a phase II study (to evaluate acute and middle-term toxicity); finally a phase III study has been started, and is still ongoing, to compare the efficacy of partial irradiation by IORT with respect to conventional radiotherapy on the whole breast. The toxicity so far detected is absolutely acceptable, but is necessary to wait for the end of the study in order to have the preliminary data, and for an adequate period of follow-up in order to evaluate the results. Eur. J. Oncol., 8 (3), 191-193, 2003

***Key words*: adjuvant radiotherapy, intraoperative radiotherapy, breast cancer**

Introduzione

La radioterapia intraoperatoria (IORT) è una tecnica speciale che consente l'erogazione di una singola frazione di radioterapia (RT) in un'area anatomica direttamente esposta durante l'intervento chirurgico. La visione diretta del bersaglio garantisce la massima precisione nella somministrazione della dose ed il risparmio degli organi sani interposti che possono essere allontanati dal fascio di radiazioni[1]. La IORT può essere utilizzata sia come unica modalità, sia come sovradosaggio seguito dal completamento del trattamento con radioterapia esterna. In questo senso ci sono numerose esperienze in letteratura riguardanti soprattutto tumori localmente avanzati[2, 3]. Il problema organizzativo, legato al

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trasporto del paziente dalla sala operatoria al bunker di trattamento di radioterapia, che ha ostacolato a lungo lo sviluppo della tecnica ed il suo impiego su vasta scala, è stato superato dall'immissione sul mercato di piccoli acceleratori mobili situati in sala operatoria.

La radiazione tipicamente usata in radioterapia intraoperatoria è costituita da un fascio di elettroni ad alta energia, collimato sull'area da trattare. I vantaggi dell'uso degli elettroni rispetto ai fotoni sono la maggiore omogeneità di distribuzione della dose e la riduzione drastica del rilascio della dose in profondità. Poche sono le esperienze che riguardano l'impiego della IORT nelle neoplasie mammarie. Tutti i trials che confrontano l'uso della RT postoperatoria dopo chirurgia conservativa del carcinoma mammario hanno mostrato un vantaggio significativo a favore del braccio di trattamento in termini di controllo locale, riducendo il tasso di recidive a 5 anni dal 27-42% al 2-20% con la RT[4]. Alcuni di questi studi hanno identificato alcuni sottogruppi a basso rischio di recidiva (ad esempio l'età anziana), anche se non si è ancora giunti ad una caratterizzazione definitiva. Nella ricerca di soluzioni alternative al trattamento adiuvante convenzionale sulla mammella, che può creare problemi legati alla tolleranza dei tessuti sani, alla accessibilità geografica ad un centro di radioterapia, alla durata relativamente lunga del trattamento, all'interazione con i trattamenti sistemici, la IORT offe numerosi vantaggi. I risultati dello studio randomizzato Milano III, che ha confrontato la QUAD versus QUART, hanno evidenziato che in un sottogruppo di pazienti con età superiore a 55 anni l'incidenza di recidive era simile nei 2 bracci di trattamento. Inoltre la maggior parte delle recidive locali (86%) si sono manifestate nello stesso quadrante operato[5]. Questa osservazione incoraggia la scelta di un trattamento più limitato con lo scopo di eliminare l'eventuale residuo di cellule tumorali nella vicinanza del focus primario.

Materiali e metodi

Nell'Istituto Europeo di Oncologia (IEO) è stato installato un acceleratore lineare mobile di elettroni, il NOVAC7, realizzato dall'Hytesys in collaborazione con l'ENEA, concepito esclusivamente per i trattamenti di IORT, che per le sue caratteristiche – peso e dimensioni ridotte, sterilizzabilità, bassa radiazione ambientale – può essere impiegato in sala operatoria senza particolari modifiche. Per ragioni radioprotezionistiche, tale sala viene protetta da schermi mobili costituiti da barriere addizionali di piombo di 2-15 cm di spessore in prossimità e sotto il tavolo operatorio[6]. I ratei di esposizione misurati negli ambienti adiacenti alla sala operatoria non superano i 50 microSV/ora.

L'esperienza clinica nell'IEO si è sviluppata in 3 fasi. Sono stati attuati una fase di *dose escalation* per definire la massima dose tollerata in singola frazione, terminata nell'aprile 2000, ed uno studio di fase II, concluso a novembre 2000, in cui le pazienti sono state trattate alla dose massima di 21 Gy, per valutare la tossicità acuta e a medio termine. I criteri di elegibilità comprendono la diagnosi istologica di tumore infiltrante, l'unifocalità ed il diametro del nodulo inferiore a 2,5 cm. Nella fase I e II sono state reclutate 101 pazienti, di cui 84 hanno ricevuto una dose intraoperatoria di 17-19-21 Gy come trattamento unico, non seguito dal completamento con RT esterna.

Nel dicembre 2000 è iniziato lo studio di fase III (Trial ELIOT) che confronta il trattamento convenzionale di radioterapia esterna (50 Gy sull'intera mammella seguita dal boost di 10 Gy) versus il trattamento con IORT alla dose di 21 Gy, con l'obiettivo primario di valutare l'efficacia del nuovo approccio in termini di controllo locale, sopravvivenza libera da malattia e globale, incidenza di metastasi a distanza, risultato cosmetico e costi. I criteri di inclusione sono i medesimi degli studi precedenti. Il trial è in corso di reclutamento e fino ad oggi sono state arruolate 257 pazienti, di cui 122 nel braccio di radioterapia esterna e 135 nel braccio IORT.

La procedura IORT si integra agevolmente con l'atto chirurgico. Dopo l'exeresi della neoplasia, la ghiandola mammaria viene mobilizzata scollandola sia nei piani superficiali che nei piani profondi, vengono inseriti dei dischi di metallo pesante a protezione della parete toracica e degli organi sottostanti, la breccia chirurgica della quadrantectomia viene suturata e si viene cosi a creare il volume bersaglio del trattamento radiante intraoperatorio, il letto tumorale più un certo margine di sicurezza. Vengono scelti il diametro e l'angolazione del collimatore più idoneo, che viene connesso alla testata dell'acceleratore e posizionato nella breccia chirurgica, e viene scelta l'energia del fascio di elettroni in relazione allo spessore della ghiandola residua. La dose di irradiazione è somministrata in un tempo relativamente breve.

Risultati

Sono disponibili i risultati dei due studi di fase I e II recentemente conclusi. Con un follow-up mediano di 18 mesi, 10 pazienti hanno mostrato una tossicità acuta di grado lieve/moderato, che comprendeva infezione (n = 2), dolore (n = 2), ematoma (n = 3), edema mammario (n = 3). Per quanto riguarda la tossicità cronica, valutata con la scala SOMALENT, sono state registrate una fibrosi di grado 3, che ha colpito una paziente sottoposta a sovradosaggio di 10 Gy con IORT seguiti da 44 Gy di radioterapia esterna su tutta la mammella, e 5 pazienti con fibrosi di grado 1-2[7].

Conclusioni

La esperienza preliminare condotta presso l'IEO con la IORT ha dato esiti soddisfacenti. La procedura è semplice e rapida, l'addestramento del personale avviene in breve tempo, gli effetti collaterali a breve e medio termine sono limitati ed il grado di soddisfazione della paziente è alto. Bisogna comunque attendere la conclusione dello studio randomizzato in atto e il necessario tempo di follow-up per valutare l'impatto a lungo termine sul controllo della malattia e sulla cosmesi.

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Eur. J. Oncol., vol. 8, n. 3, pp. 195-197, 2003

Caratteri ultrastrutturali delle cellule di piccola taglia nei meningiomi tipici e atipici

Ultrastructural characters of small cells in typical and atypical meningiomas

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Riassunto

Finalità. **Nel contesto di meningiomi sinciziali o transizionali tipici e atipici sono presenti elementi di piccola taglia, caratterizzati da scarso citoplasma e nucleo denso, ipercromatinico. Essi si ritrovano in numero variabile da caso a caso e sono distribuiti in modo apparentemente disordinato.** ***Materiale e metodi.*** **Sono stati studiati al microscopio elettronico a trasmissione 50 casi di meningiomi di cui 20 sinciziali, 20 transizionali e 10 atipici, per definire la ultrastruttura delle cellule di piccola taglia.** ***Risultati.*** **Gli Autori hanno documentato che, a differenza delle cellule meningoteliali, tali elementi sono privi di prolungamenti citoplasmatici, di interdigitazioni e di filamenti intermedi.** ***Conclusioni.*** **I caratteri citologici hanno permesso di formulare alcune ipotesi circa la natura e l'istogenesi di tali cellule. Eur. J. Oncol., 8 (3), 195-197, 2003**

Parole chiave**: cellule di piccola taglia, interdigitazioni, desmosomi, filamenti intermedi**

Summary

Aim. **Within the context of typical and atypical syncytial or transitional meningiomas, some small cells are present, characterized by a scanty cytoplasm and hyperchromatinic, dense nucleus. They are found in varying numbers from case to case and seem to be randomly distributed.** ***Materials and methods.*** **50 cases of meningioma, 20 of which syncytial, 20 transitional and 10 atypical, were studied by transmission electron microscope, to investigate the ultrastructure of the small cells.** ***Results.*** **The Authors showed that, unlike meningothelial cells, these cells are devoid of cytoplasm projections, junctions and intermediate filaments.** ***Conclusions.*** **The cytological features of these cells have allowed some hypotheses to be made on their nature and histogenesis. Eur. J. Oncol., 8 (3), 195-197, 2003**

Key words**: small cells, junctions, desmosomes, intermediate filaments**

Introduzione

I meningiomi sinciziali e transizionali sono le varietà istologiche più frequenti nell'ambito di questi tumori.

Come è noto, le forme sinciziali sono costituite solo da cellule meningo-endoteliali; quelle transizionali sono formate da due subpopolazioni: una è rappresentata da cellule meningo-endoteliali, l'altra da elementi allungati, riconoscibili come fibroblasti.

Accanto alle suddette forme tipiche sono descritti meningiomi sinciziali e transizionali atipici; questi sono identificabili per uno stato di ipercellularità, per un aumentato indice mitotico, per l'esistenza di micronecrosi, per il polimorfismo cellulare, per le atipie nucleari, nonché per le modalità di crescita sotto forma di sottili lamine monocellulari[1-3]. Attraverso la microscopia elettronica sono stati evidenziati alcuni caratteri peculiari delle cellule meningo-endoteliomatose; questi sono rappresentati dalle interdigitazioni citoplasmatiche, dalla presenza di desmosomi e di emidesmosomi, dalla esistenza di fasci di filamenti intermedi che si rivelano vimentina-positivi[4].

Nell'ambito di questi meningiomi, tipici o atipici, si repertano elementi cellulari di piccola taglia aventi nucleo denso e ipercromatinico. Questi elementi, in numero variabile da caso a caso, sono distribuiti in modo apparentemente disordinato; essi sono forniti di scarso citoplasma, hanno forma sferoidale od ovoidale e sono riconoscibili agevolmente poiché sono forniti di un nucleo compatto ed ipercromatinico, differente dai nuclei vescicolosi delle cellule circostanti.

Questi elementi di piccola taglia si differenziano da eventuali

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infiltrazioni linfocitarie per la loro maggiore volumetria e per i caratteri nucleari. Il loro significato rimane tutt'ora oscuro e in letteratura non è stata loro dedicata particolare attenzione.

Per tali motivi gli Autori ritengono utile apportare un contributo alla conoscenza di tali cellule.

Materiale e metodi

Per questo studio sono stati utilizzati 50 casi di meningiomi: 20 di tipo sinciziale, 20 di tipo transizionale e 10 atipici.

Dai campioni in esame sono stati prelevati macroframmenti per la microscopia luce; questi sono stati fissati in formalina tamponata al 10% e dopo processazione sono stati colorati con ematossilina-eosina, e. Van Gieson, Azan-Mallory per il connettivo, PAS.

Contemporaneamente e contestualmente sono stati prelevati dai medesimi campioni numerosi microframmenti, i quali sono stati fissati in paraformaldeide tamponata al 4% a pH 7,2, post-fissati con una soluzione di osmio al 2%, e quindi inclusi in Epon.

Da tali blocchetti sono state allestite sezioni semifini, colorate con blu di toluidina. Dopo un esame preliminare al microscopio luce delle sezioni semifini così allestite, sono state preparate sezioni sottili che, dopo essere state contrastate con acetato di uranile e citrato di piombo, sono state osservate al microscopio elettronico a trasmissione.

Risultati

Microscopia luce

Al microscopio luce i casi in esame evidenziano una architettura istopatologica specifica di tali tumori: il disegno architettonico, la densità cellulare, la tipologia cellulare esprimono, a seconda dei singoli casi in esame, il profilo microscopico dei meningiomi tipici sinciziali, di quelli tipici transizionali e di quelli atipici.

Nel contesto delle suddette popolazioni cellulari si repertano elementi di taglia inferiore rispetto alla restante popolazione; tali elementi sono rintracciabili con difficoltà se sono distribuiti singolarmente o sono mascherati dalla circostante popolazione cellulare; sono invece facilmente riconoscibili se sono raccolti in nidi (fig. 1). Pur essendo di piccole dimensioni, essi sono identificabili per la densità cromatinica dei loro nuclei, e per la loro forma rotondeggiante; frequentemente sono tra loro a mutuo contatto senza mostrare strutture giunzionali, hanno margini cellulari ben netti, sono forniti di un'esigua quota di citoplasma e sono centrati da un nucleo iperdenso e compatto (fig. 2). Il numero di tali cellule varia non solo da caso a caso, ma anche in zone diverse dello stesso caso e la loro distribuzione topografica è casuale, asimmetrica, per concentrazioni molto diversificate da campo a campo nell'ambito dello stesso caso.

In nessun caso sono stati osservati rapporti topografici preferenziali o esclusivi con strutture vasculo-stromali.

Microscopia elettronica

Le cellule di media e grossa taglia presentano, anche se in modo variabile, i caratteri ultrastrutturali della cellula meningea sin-

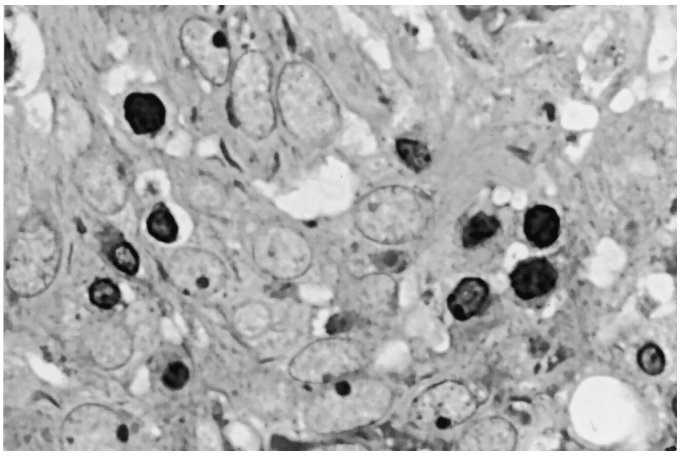

Fig. 1. Meningioma sinciziale tipico. Nell'ambito di cellule meningoteliali, fornite di nuclei vescicolosi, si repertano elementi con nuclei sferoidali, ipercromatinici e con un'esigua quota citoplasmatica. Semifina - Blu di toluidina, 200x.

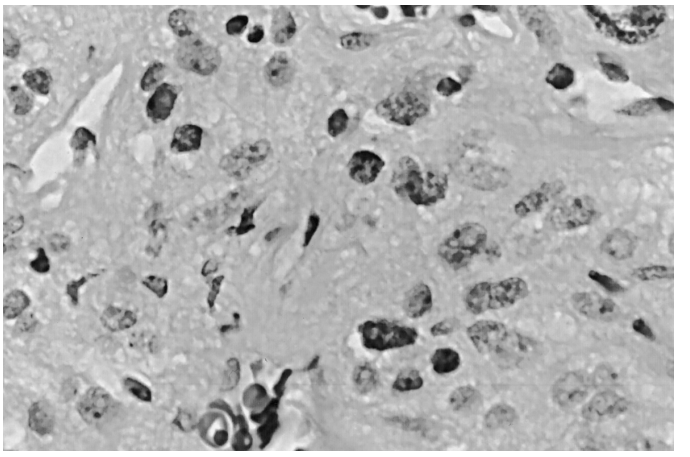

Fig. 2. Meningioma sinciziale atipico. Nel contesto di una popolazione cellulare meningoteliale con nuclei irregolari, si repertano cellule aventi nuclei sferoidali e ipercromatinici. Semifina- Blu di toluidina, 100x.

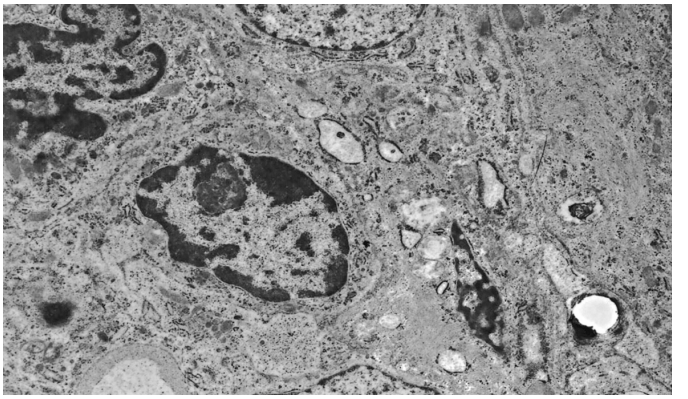

Fig. 3. Meningioma sinciziale tipico. Presenza di elementi di piccola taglia con cromatina addensata, con scarso citoplasma. TEM, 7000x.

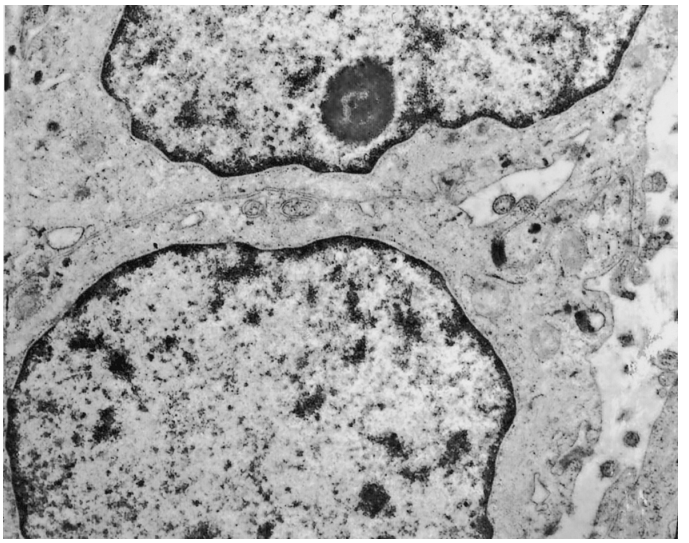

Fig. 4. Meningioma sinciziale tipico. Presenza di elementi di piccola taglia, il loro citoplasma è esiguo, povero di organuli ed è privo di filamenti intermedi. TEM, 12000x.

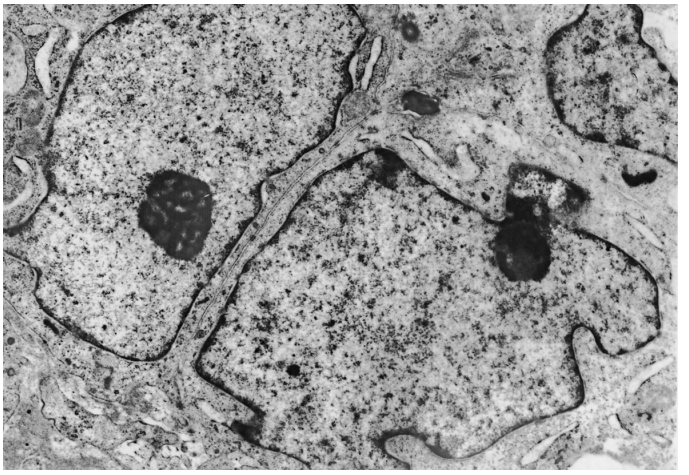

Fig. 5. Meningioma sinciziale tipico. Cellule di piccola taglia; sono prive di prolungamenti citoplasmatici e di interdigitazioni. Le superfici sono combacianti in modo rettilineo. TEM, 12000x.

ciziale; in particolare, sono ben evidenti le digitazioni intercellulari, le strutture giunzionali, nonché l'esistenza di una ricca componente di organuli intracitoplasmatici; inoltre si osservano numerosi fasci di filamenti intermedi: il loro numero si modifica in rapporto al grado di differenziazione della popolazione cellulare.

Le cellule di piccola taglia, sebbene siano commiste alle precedenti, si riconoscono agevolmente per l'assenza di prolungamenti citoplasmatici, e per la presenza di una membrana cellulare ben demarcata e con profilo appianato (fig. 3, 4). Nei campi microscopici nei quali si raccolgono in piccoli aggregati, le cellule sono a mutuo contatto, tra loro adese, ma prive di coesione per assenza di strutture giunzionali (fig. 5). Il loro citoplasma è esiguo, e spesso si riduce ad un semplice orletto perinucleare; esso ha un aspetto uniformemente compatto e contiene qualche raro organulo e pochi granuli ribosomiali dispersi; in nessun campo sono evidenziabili strutture riferibili a filamenti intermedi.

Conclusioni

Queste cellule di piccola taglia hanno caratteri citologici molto semplificati: sono molto diverse dagli elementi meningo-endoteliali in quanto sono prive di strutture giunzionali, di interdigitazioni e di filamenti intermedi e sono persino povere di organuli intracitoplasmatici.

Questi caratteri citologici non forniscono indicazioni riguardanti la loro istogenesi ed il loro significato, né emergono indicazioni dalle osservazioni riguardanti la loro distribuzione topografica o la loro concentrazione per unità di superficie. Infatti è stato possibile constatare che la loro topografia è casuale, poiché non si notano posizioni preferenziali in rapporto ai vasi o a strutture stromali; il loro numero si accresce nei meningiomi in attività proliferativa od atipici.

Circa la natura di tali cellule sono possibili tre ipotesi interpretative: la prima è quella di considerare tali elementi come cellule meningo-endoteliali scarsamente differenziate o come cellule staminali delle cellule aracnoidali. Secondo tale opinione esse rappresenterebbero elementi di crescita e di aggressività biologica di questi tumori. Tale ipotesi non appare sostenibile poiché la densità numerica di tali elementi è del tutto casuale e comunque aumenta lievemente nei meningiomi atipici.

La seconda ipotesi, sostenuta da Mirra e Miles[5] e da Akdemir *et al*[6], è quella di considerare tali cellule come periciti. Secondo tali Autori nei meningiomi si repertano cellule piccole e dense, le quali sono in parte circondate da abbozzi di membrana basale e quasi sempre sono a ridosso di capillari.

Anche questa ipotesi non appare convincente, poiché tali cellule, nei casi in esame, non sono sempre costeggiate da frammenti di membrana basale, né prediligono le zone perivascolari.

La terza ipotesi prende in considerazione l'anatomia microscopica dell' aracnoide normale: è noto che tale meninge è rivestita in superficie da cellule aracnoidali (aventi gli stessi caratteri citologici riprodotti nei meningiomi sinciziali); oltre tale citotipo, si repertano al di sotto della membrana basale sia cellule reticolari aracnoidali sia elementi piccoli di forma rotondeggiante od ovoidale, che hanno scarso citoplasma e nucleo denso, compatto, ipercromatinico[7]. Secondo questa ipotesi le cellule di piccola taglia presenti nei meningiomi corrisponderebbero ai suddetti elementi dell'aracnoide normale.

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Cancer among the black labour force of the platinum group metals and the gold mining industries in South Africa, 1989-96

I tumori fra i lavoratori neri nelle industrie minerarie dei metalli del gruppo del platino e dell'oro in Sud Africa, 1989-96

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Summary

Aim. **This paper aims to quantify for the first time the cancer occurrence among black employees of the platinum group metals (PGM) industry and to compare these figures with those of the well-recorded and long established gold mining industry.** ***Patients and methods.*** **Data on cancer incidence have been obtained from records of hospitals which serve the two industries for the period 1989-96. The PGM industry employs about one quarter of the labour force of the gold mines and both industries employ men from several areas across southern Africa. The PGM industry recruits especially from Bophuthatswana; both industries employ Mozambique men and gold miners also come especially from Lesotho and Transkei.** ***Results.*** **For total cancers of all sites, PGM workers record very significantly few cases: 149 observed whereas 385 were expected. Significant deficits of cancer amongst PGM men apply to twelve specific sites, including the three most numerous cancers of gold miners, respiratory system, liver and oesophagus which are all very significantly (p <0.01) under-represented in PGM employees. Studies show that cancer of the buccal cavity has risen considerably in the black gold miners in the last forty years: this cancer is also common in the PGM workers. All sites of cancer and buccal cancer are each diagnosed at similar ages in the PGM group as in the gold industry men.** ***Conclusion.*** **These major contrasts of cancer between two extractive industries in South Africa are suggestive of occupational or environmental differences. No obvious carcinogenic risk has been suggested to exist in either industry, and specific enquiry is warranted to explain the low overall cancer incidence among the PGM's largely Tswana workforce. Eur. J. Oncol., 8 (3), 199-204, 2003**

Key words**: cancer, platinum and gold miners, South Africa**

Riassunto

Finalità. **Questo lavoro cerca di quantificare per la prima volta l'incidenza dei tumori tra i lavoratori neri delle industrie minerarie di metalli del gruppo del platino (PGM) e di confrontarne l'andamento con quello, accuratamente registrato e da lungo tempo noto, nei lavoratori delle industrie minerarie dell'oro.** ***Pazienti e metodi.*** **I dati sull'incidenza dei tumori nel periodo 1989-96 sono stati ottenuti dagli archivi degli ospedali che servono le due aree minerarie. Le industrie minerarie di PGM occupano circa un quarto del numero di lavoratori delle miniere d'oro, ed entrambe le attività minerarie occupano lavoratori provenienti da diverse aree dell'Africa meridionale. Le industrie minerarie di PGM reclutano personale soprattutto dal Bophuthatswana; in entrambe le attività estrattive sono occupati lavoratori del Mozambico, e gli addetti alle miniere d'oro vengono in numero consistente anche da Lesotho e Transkei.** ***Risultati*****. Per tutti i tumori di tutte le sedi i lavoratori dei PGM registrano, con dati altamente significativi, pochi casi: 149 osservati contro i 385 attesi. L'incidenza significativamente bassa dei tumori tra i lavoratori dei PGM riguarda dodici sedi specifiche, compresi i tre tumori più frequenti nei lavoratori delle miniere d'oro, quelli dell'apparato respiratorio, del fegato e dell'esofago, che sono tutti sotto-rappresentati in modo significativo (p <0,01) tra i lavoratori dei PGM. Gli studi mostrano che i tumori del cavo orale sono notevolmente aumentati tra i lavoratori neri delle miniere d'oro negli ultimi 40 anni: questi tumori sono comuni anche tra i lavoratori dei PGM. I tumori di tutte le sedi e quelli del cavo orale sono diagnosticati in età simili nel gruppo PGM ed in quello delle miniere d'oro.** ***Conclusioni.*** **Queste notevoli differenze nell'insorgenza dei tumori fra le due attività minerarie del Sud Africa sono indicative di differenze professionali o ambientali. Nessun rischio cancerogeno evidente è stato suggerito nei due casi, e sono indispensabili ricerche mirate per spiegare la bassa incidenza globale di tumori tra i lavoratori dei PGM principalmente del gruppo etnico Tswana. Eur. J. Oncol., 8 (3), 199-204, 2003**

Parole chiave**: tumori, minatori del platino e dell'oro, Sud Africa**

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Introduction

Our purpose is to throw initial light upon the previously unrecorded cancer patterns experienced in a major occupational group in South Africa, the black platinum group metal (PGM) workers. These patterns are compared with contemporaneous data from recent black gold miners' morbidity[1,2]. The long term aim would be to employ these analyses, whether there be contrasts or similarities of rates or of sites of cancer, towards an understanding of the causes of the cancers and thereby to seek to prevent them.

The platinum group metals' industry

PGMs consist of six chemically similar elements which, in South Africa, occur together with base metals in three different layers of the Bushveld geological complex which underlies much of the former Transvaal province. Platinum, by far the most valuable of the PGMs, was discovered in 1924 and limited production started two years later. Industrial exploitation started energetically in the 1970s and by 1988 and 1989 South Africa was already the world's leading producer[3]. In mid-February 2003 platinum values stood at $US 688 per fine ounce and palladium at $US 252.5. Platinum values exceed those of gold ($US 356.3) and, as for some time in the past, platinum has overtaken gold as the highest valued export commodity in South Africa[4]. The world demand for platinum has been boosted by the jewellery industry in Japan and by the autocatalyst industry spurred by stricter emission legislation in European Union countries[5].

The mining areas are largely concentrated in an east-west line close to Rustenburg, 110 km west-north-west of Johannesburg, and mines are under development north of Belfast in the north-east (fig. 1). New developments have increased demand for labour especially since 1989 (fig. 2) and also imply a prospect of change of ethnic composition of the labour force as the new mines are close to the home areas of differing ethnic groups. The decline in employee numbers more recently is attributable to weakening prices for PGMs during the 1990s[5].

Materials and methods

Defining the population at risk

Data concerning total populations recruited to work in the PGM industries were provided on diskette by The Employment Bureau of Africa (TEBA) by year and by territory and by former South African province or homeland of origin. As well as containing no data on age, these figures provide no information on specific locality of home address, often an important indicator. Consequently, for comparative purposes, the only details for gold miners which have been used in these analyses are those equivalent to those available for PGM workers.

For the specific period, 1989-96, the total PGM miners' figure has been reduced by 12% to exclude the Chamber of Mines' estimate of the number of white miners in the industry in those years.

The early labour force of black PGM workers from 1970 to 1976 was recorded by origin only under the four "old" provinces: Cape, Natal, Orange Free State and Transvaal. From 1977 onwards, an additional 18 territories of recruitment were added to the record. The total of men employed, mostly young, rose to 35,500 in 1974 and then, after a slight dip in 1982-3, increased to an estimated 91,700 in 1991(fig. 2).

Additional employee numbers from 1989 onwards are explained by the industry's reaction to growing market demand in Europe and Japan and consequent rise in the price of platinum, palladium and rhodium which led to new mines and increased activity in the industry[5].

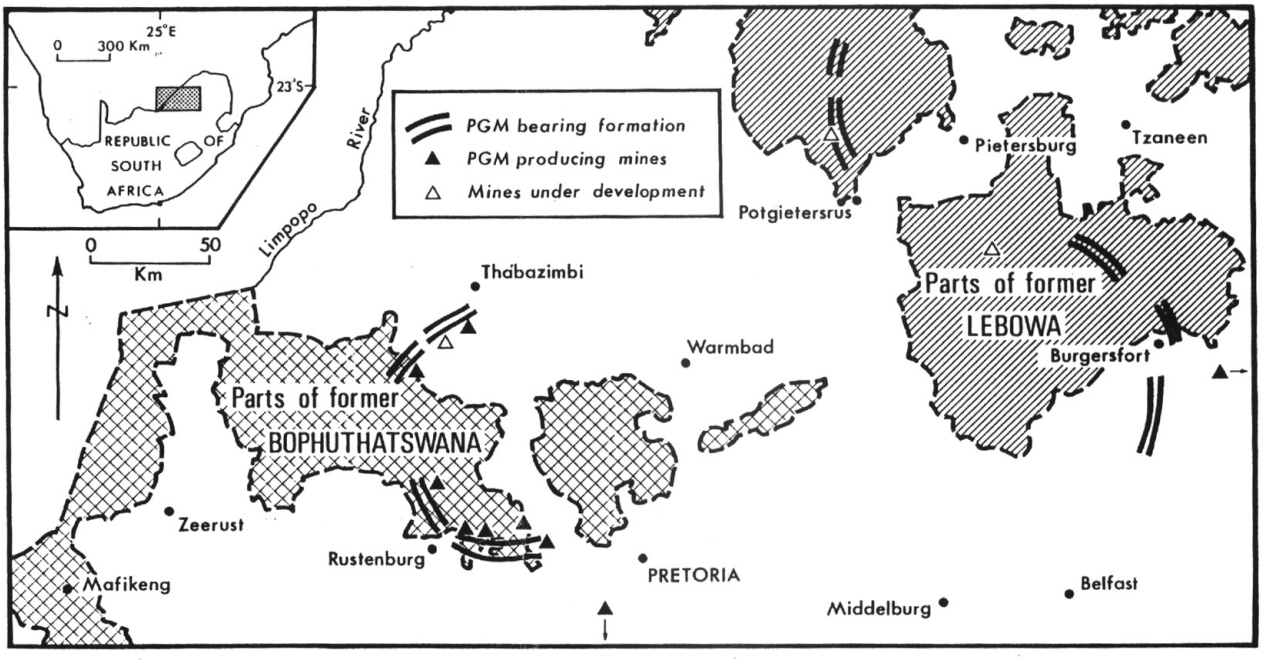

Fig. 1. Mining areas of PGM in South Africa.

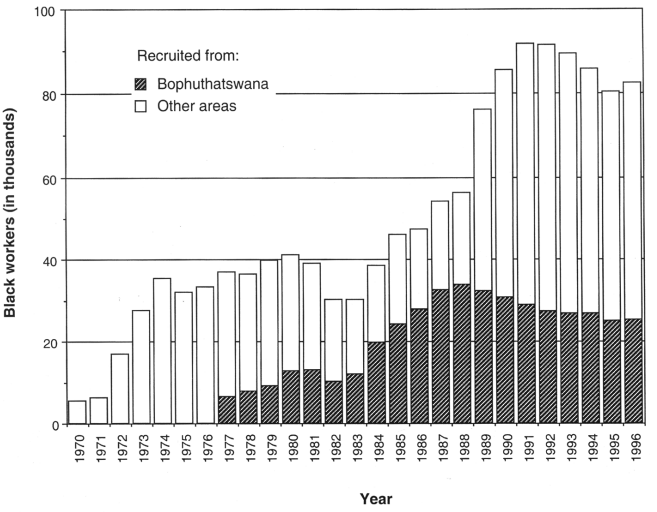

Fig. 2. Estimated black employment in South African PGM mines and operations from 1970-1996.

At the scale of territory of origin, 1987, the last year before the start of the study, saw men from Bophuthatswana total 32,300 workers out of an overall total of 56,400 (42%). Additionally 1100 men (2%), listed as from the Cape, were likely to be from the northern Cape and therefore Tswana by ethnic group. By 1996 Bophuthatswana provided some 25,000 of the total of 82,200, still above 30% of the total labour force in the industry.

Based on TEBA data for the six years 1989-1994 and rescaled for the study period 1989-96, Mozambique (6.9%) has recently increased its share of PGM employees, overtaking both Transkei (6.8%) and Lesotho (5.8%). Thus the labour force from the former Bophuthatswana has long been the dominant ethnic group in the PGM industry, together with the traditional suppliers to the mines' industries, Mozambique, Transkei and Lesotho. Altogether, over half of all PGM workers came from the above four areas (fig. 3). More recently, emphasis has been laid upon nearby places, Botswana and areas in the former Transvaal.

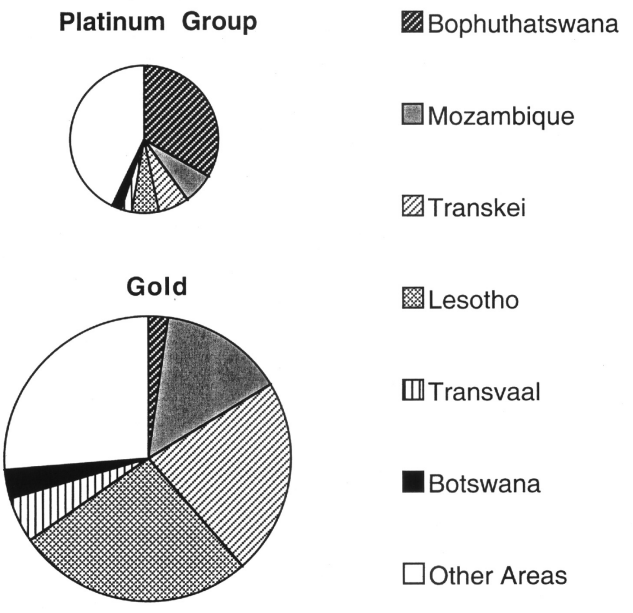

Fig. 3. Principal territories of origin of southern Africa's black mineworkers (estimated for PGM workers from TEBA's figures for 1989-94).

The major differences in recruitment between the PGM industry and the far larger gold mining industry are the fourfold greater total labour force in the gold mines and the comparatively smaller proportion of miners (2.2%) from Bophuthatswana in the gold industry. In each industry's total labour force, the gold mines recruited more than twice as many by percentage from each of Mozambique, Transkei and Lesotho. Moreover, whilst the age breakdown of the gold labour force is known, that of the PGM miners is not available either by year of birth or by age at recruitment.

Recording black miners' cancer cases

Because individual mine hospital records were not available for analysis, cancer case records of black workers in the PGM industry (excluding benign tumours), including age at diagnosis, were derived from the industry's main referral hospital, the now defunct SelbyPark Memorial Centre (SPMC) in Johannesburg, which had 650 beds and 24-hour specialist medical and surgical services. It is estimated that over 85% of cancer cases were referred by other hospitals serving the PGM industry to SPMC. This implies that figures used here possibly slightly under-estimate actual case numbers. However the quality of diagnosis at SPMC was excellent, with close to 100% histopathological confirmation.

In order to compare the two industries, cancer case data (excluding benign tumours) for all black mineworkers in the entire gold mining industry were derived for 1989 to 1996 from the five major mine hospital records and from the SPMC.

Results

Crude incidence (morbidity) rates (CIRs) were calculated for the period 1989-96 for both the PGM and the gold industry for each site of cancer.

Comparison of cancer case numbers and rates in the PGM and the gold labour forces are given in Table 1. Against the null hypothesis that men of each industry are from populations similarly liable to cancer, significance tests (with no allowance for age) are also tabulated against the Poisson distribution at $p < 0.05$ and $p < 0.01$.

Cases in PGM workers and in gold miners have been considered for 1989-1996 for fifteen major sites of cancer, "other and unspecified sites" and total cancers. Black workers on PGM mines recorded 149 cases of these cancer sites out of 1,894 in both industries (7.9%), whereas PGM could have been expected *pro rata* to their 21.0% of all workers in both industries to show 398 cases. Black workers in the PGM industry thus recorded a very significantly lower risk of cancer of all sites taken together ($p < 0.01$) than their gold mining equivalents.

The PGM workers record, as their most numerous site of cancer, tumours of the buccal cavity (ICD 140-149). The most numerous sub-site within this small sample is tongue (ICD 141) with 8 cases out of 24 (33.3%). This conforms with the proportion found in the population at large in South Africa[6], and also in Canada[7].

Table 1 - Observed cases and CIRs of major cancers among black labour in the PGM and gold mining industries, 1989-96[a]

ICD	Site	PGM miners		Gold miners[2]		Total obs (PGM + gold)	Expected among PGM	Poisson significance (p <)[b]
		Obs	CIR	Obs	CIR			
140-149	Buccal cavity	24	3.5	94	3.7	118	24.8	NS
150	Oesophagus	11	1.6	198	7.7	209	43.9	0.01
151	Stomach	3	0.4	49	1.9	52	10.9	0.01
153-154	Colorectal	6	0.9	58	2.3	64	13.5	0.05
155	Hepatocellular carcinoma	19	2.8	223	8.7	242	50.9	0.01
157	Pancreas	3	0.4	33	1.3	36	7.6	NS
161	Larynx	4	0.6	66	2.6	70	14.7	0.01
162	Respiratory system	5	0.7	241	9.4	246	51.7	0.01
171.9	Kaposi's sarcoma	8	1.2	28	1.1	36	7.6	NS
172	Melanoma	1	0.1	21	0.8	22	4.6	0.05
185	Prostate	1	0.1	49	1.9	50	10.5	0.01
191-192	Brain/central nervous system	2	0.3	30	1.2	32	6.7	0.05
200-2	Lymphomas	20	2.9	128	5.0	148	31.1	0.05
203	Myeloma	4	0.6	52	2.0	56	11.8	0.01
204-208	Leukaemia	17	2.5	57	2.2	74	15.6	NS
239	Other and unspecified	21	3.1	418	16.3	439	92.3	0.01
	All cancers	149	21.8	1745	68.1	1894	398.2	0.01

[a] Estimated 8 year total black labour force: PGM 682,000 man-years (21.0%), gold 2,562,000 man-years.
[b] NS = PGM workers' observed (obs) and expected cases not significantly different.

The small population of the northern Cape division showed 17 tongue cancers in the National Registries for 1989, 90 and 91[6, 8]. Table 2 also shows that PGM workers' records for cases of other intra-oral sites of cancer are too uncommon or too unspecific to compare with the national figures. However, the PGM and the national registry data sets have unspecific "other" buccal sites in similar proportions. Buccal cavity cancers have increased from 2.0% of all cancers in gold miners in the '60s[9] and '70s[10] to 5.2% in the '90s[1]. If the high proportion of buccal cavity cancers in PGM workers is included with the gold miners (see "Total Observed" in Table 1), this figure becomes 6.2%: 118 buccal cavity cancers among 1,894 all sites of cancer in eight years.

Table 1 shows that a large number of other sites of cancer are very significantly under-represented in PGM workers as compared to gold miners and only two sites, leukaemia and Kaposi's sarcoma, are actually more common in the PGM group. This result may well imply that HIV/AIDS is equally established in both industries. Of particular importance, the three most numerous sites in gold miners – liver, respiratory system and oesophagus – each with a CIR of over 7 per 100,000 man-years, are all very significantly less common in PGM workers, with CIRs of less than 3/100,000.

Similarly, lymphatic, stomach, myeloma, larynx, melanoma, colorectal, brain/CNS and prostate cancers are all low in the PGM workforce. Overall then, these analyses provide evidence of a far lower burden of cancer in workers of the more recently developed PGM industry than in the old established gold industry labour force. Only one other site of cancer besides buccal cavity, Kaposi's sarcoma and leukaemia, namely pancreas, shows rates for PGM workers not significantly different from those of the gold miners.

Several sites of cancer known to be relatively less common among gold miners, are not recorded at all among the PGM workers and so are omitted from these comparisons. These include connective tissue, thyroid, bone, bladder, kidney, testis, pleura and penis.

Ages at time of cancer diagnosis

Since age at diagnosis has been suggested as possibly bearing upon the PGM workers' low rates of cancers, age is now specifically addressed. Availability of data concerning the miners is uneven, since the PGM industry ages of the labour force are not available but ages of cancer cases are. For gold miners the ages of

Table 2 - Buccal cavity cancer in black PGM workers in South Africa compared to National Registry figures

ICD	Site	PGM miners 1989-96		National Cancer Registry of South Africa 1989[8]		1990-1991[6]	
		No.	%	No.	%	No.	%
140	Lip	1	4.2	35	4.0	55	2.6
141	Tongue	8	33.3	240	27.4	558	26.1
142	Salivary glands	-	-	20	2.3	93	4.3
143	Gum	-	-	28	3.2	76	3.5
144	Floor of mouth	5	20.8	-	-	-	-
145, 149	Other and unspecified	9	37.5	309	35.3	719	33.6
147	Nasopharynx	1	4.2	243	27.8	641	29.9
	Total	24	100.0	875	100.0	2142	100.0

Table 3 - Estimated ages of black workers at cancer diagnosis (by number and percent of cases with ages known)

Age (years)	All sites of cancer						Cancer of buccal cavity					
	PGM 1989-96		Gold 1989-96[2]		National rates 1990-91[6]		PGM 1989-96		Gold 1989-96		National rates 1990-91	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Under 29	22	15.7	89	7.3	1982	9.8	1	4.8	2	3.0	101	4.9
30-34	11	7.9	110	9.0	692	3.4	1	4.8	5	7.5	45	2.2
35-39	21	15.0	150	12.2	901	4.4	1	4.8	5	7.5	83	4.0
40-44	23	16.4	183	14.9	1467	7.2	1	4.8	11	16.4	148	7.2
45-49	23	16.4	218	17.8	1808	8.9	6	28.6	9	13.4	203	9.8
All under 50	100	71.4	750	61.2	6850	33.7	10	47.6	32	47.8	580	28.1
50-54	17	12.1	218	17.8	2494	12.3	5	23.8	17	25.3	288	14.0
55-59	15	10.7	183	14.9	2364	11.6	4	19.0	17	25.3	299	14.5
60-64	4	2.9	58	4.7	2945	14.5	-	-	-	-	338	16.4
65-99	4	2.9	16	1.3	5650	27.8	2	9.5	1	1.6	559	27.0
Age known	140	100.0	1225	99.9	20303	99.9	21	99.9	67	100.0	2064	100.0
Age not known	9	-	520	-	1060	-	3	-	27	-	80	-
Total	149	-	1745	-	21363	-	24	-	94	-	2144	-

both the labour force and of cancer cases are available. Table 3 employs both the gold miners' cancers at known ages as well as the National Registry's figures[6] as referent rates of all cancers and of buccal cancers, rather than comparing the PGM workers solely with those of the gold industry.

All sites of cancer by age

In Table 3 PGM workers' cancers of all sites by age are given as a percentage of all those PGM cancers whose ages are known. Also given is the national black male percentage of all cancers at ages. Table 3 emphasises the young ages of the PGM workers at time of diagnosis of all cancers against the national experience in 1990-91[6]. In fact 71.4% of all PGM workers' cancers are diagnosed under 50 years of age whereas the national figure at this age is as low as 33.7% (see indented subtotals in line 6 of Table 3). The highest percentage of all sites of cancers diagnosed in the national figures are from 50 years and upwards, whereas at that age all PGM cancer rates are starting to decline. Gold miners with 61.2% of all cancers diagnosed below 50 years lie between the two extremes.

Cancer of the buccal cavity by age

The second section of Table 3 also shows the percentage of buccal cancer by age, firstly among the PGM workers. Data about age of diagnosis of buccal cancers in the gold miners' population over the same period show an exactly similar proportion of these cases in each of the extractive industries at 47.8% under 50, whereas the national figure has 71.9% significantly older than 50 years. A further half of all buccal cavity cancers in the PGM workers occur in the 50-59 age groups, which are again far younger than the national figures record.

Discussion and conclusion

The study described here is a selective overview in the sense that the data were drawn from the central hospital to which PGM cancer cases were referred from the individual mine hospitals after diagnosis. Unfortunately, detailed district records of the origins of patients in these hospitals are not available, with the result that the home location address of each PGM cancer case was not accessible for geographical analysis. Nor is the age breakdown of the whole PGM workforce available.

With less than a dozen cases of cancer in 8 years among an estimated 682,000 man-years of black workers in the PGM industry for each site of cancer except buccal cavity, liver, lymphoma and leukaemia, the above data can scarcely support any broad theorising about causation, nor about confounding factors. For example, arsenic or other contaminant exposures might usefully be considered. Furthermore, apart from hypersensitivity due to exposure to platinum salts, no human or experimental data are available to assess the health risks in either PGM or gold mining; for instance, the potential for carcinogenicity of platinum and platinum compounds, except for cisplatin, which is used therapeutically[11]. All that can be said at present is that this workforce has significantly fewer cases of cancer than the gold miners and is drawn particularly from ethnic groups of the northern Cape and Bophuthatswana who are barely represented on the gold mines. Also, buccal cavity cancer occurs at an earlier age in both PGM workers and in gold miners than in the National Registry and is generally on the increase in the mining groups' employees.

Further enquiry is warranted to seek explanation for the contrasted occurrence of cancer in the two industries, superficially similar but with dissimilar mixes of places of origin among their workers. Such enquiry should include socio-economic and customary home backgrounds of the labour force particularly among the Tswana people, as well as the actual type of job carried out by each patient in the PGM industry.

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L'approccio globale alle necessità del paziente oncologico: risultati di uno studio prospettico[a]

The global approach to the needs of the cancer patient: results of a prospective study

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Riassunto

Presso l'Unità Operativa (UO) di Oncologia degli Ospedali di Gorizia e di Monfalcone, allo scopo di realizzare un approccio globale al malato oncologico e di conoscere i principali problemi del malato e della sua famiglia, e quindi di adottare i provvedimenti più attinenti, è stato condotto uno studio prospettico che ha utilizzato due questionari preparati *ad hoc* da un gruppo di studio misto composto da un medico oncologo, da un'infermiera professionale oncologa, da cinque pazienti e da una giovane vedova. Dal lavoro di gruppo sono emersi, come temi più sentiti, la comunicazione della diagnosi, l'informazione, il coinvolgimento della famiglia, il tempo trascorso tra i primi sintomi della malattia e l'inizio degli accertamenti (tempo diagnostico), il tempo trascorso tra la diagnosi e l'inizio della terapia (tempo terapeutico), il contatto del paziente con altri malati affetti da cancro. Tutti questi argomenti sono stati affrontati con i questionari preparati dal gruppo, che sono stati somministrati rispettivamente 2-3 settimane dopo la prima visita presso l'UO di Oncologia e dopo 3-6 mesi. Sono stati valutati 138 primi e 43 secondi questionari. I principali dati emersi dallo studio sono stati la pluralità della comunicazione della diagnosi di tumore, il precoce coinvolgimento della famiglia sia nella comunicazione della diagnosi che nel ruolo di sostegno, le buone relazioni con il personale sanitario, il discreto giudizio sulla completezza dell'informazione, la variabilità delle reazioni psicologiche, la scarsa informazione sulla possibilità di usufruire di sostegno da parte delle associazioni di volontariato, la relativa brevità dei tempi diagnostico e terapeutico, le rilevanti ricadute sociali e lavorative. Eur. J. Oncol., 8 (3), 205-209, 2003

Parole chiave: **approccio globale, malato oncologico, famiglia, rete**

Summary

A prospective study on the global approach to the cancer patient and on his needs and those of his family has been performed at the Oncology Operative Unit of the Gorizia and Monfalcone Hospitals. For this prospective study two questionnaires have been drawn up by a mixed working group composed of five patients, a young widow, an oncologist and a specialist oncology nurse. This study has shown that the most important aspects are communication of the diagnosis, information, family involvement, time spent from the first symptoms of disease to diagnosis, time spent from the diagnosis to the beginning of therapy, and the relationships with other cancer patients. All these items were taken into consideration by the two questionnaires, submitted 2-3 weeks after the first visit at the Oncology Unit and 3-6 months thereafter, respectively. 138 first and 43 second questionnaires have been evaluated. Main results have been the plurality of the communication of diagnosis, the early involvement of the family in both the communication of diagnosis and supportive rôle, a good relationship with the personnel of the health unit, the quite positive judgement on the adequacy of the information, the variability of the psychological reactions, the limited information on the availability of the voluntary associations, the rather short diagnosis and therapy times, the important social and working consequences. Eur. J. Oncol., 8 (3), 205-209, 2003

Key words: **global approach, cancer patient, family, network**

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Introduzione

È noto come la malattia neoplastica si accompagni, al di là e spesso indipendentemente dalla sua gravità, anche a rilevanti ricadute su vari aspetti della vita del malato e della sua famiglia. Infatti, oltre a quella sanitaria, anche le sfere psicologica, familiare, economica e sociale vengono pesantemente influenzate. Mentre in passato l'attenzione prestata ai problemi non strettamente sanitari era limitata, ora, e sempre di più, si sta diffondendo la consapevolezza che, per dare una risposta completa, è necessario affrontare in maniera globale i problemi del malato neoplastico e della sua famiglia.

Questo atteggiamento si rivela particolarmente opportuno nei pazienti oncologici seguiti presso i centri periferici, pazienti non selezionati, spesso anziani ed affetti da altre patologie, nei quali i problemi concomitanti assumono una particolare rilevanza. Un approccio globale al malato oncologico richiede però una conoscenza approfondita delle sue problematiche, per ottenere la quale è necessario disporre di un questionario dedicato, non standardizzato, e strettamente attinente alle caratteristiche della popolazione che viene seguita. Per tale motivo, presso l'Unità Operativa (UO) di Oncologia dell'Ospedale di Monfalcone e di Gorizia, è stato intrapreso lo studio prospettico che viene presentato in questo lavoro, con lo scopo di valutare i bisogni del malato avvalendosi, per la ricerca, di un contributo fondamentale degli stessi pazienti e dei loro familiari.

Materiali e metodi

Lo studio è stato suddiviso in quattro fasi:
1) costituzione di un gruppo di studio misto composto da malati, familiari, personale dell'UO di Oncologia;
2) preparazione di due questionari, il primo da somministrare al momento della diagnosi, il secondo dopo tre-sei mesi;
3) distribuzione dei questionari;
4) valutazione dei risultati dei questionari.

Il gruppo di studio misto

Il gruppo di studio era costituito da cinque pazienti, da un familiare, da un'infermiera professionale e da un medico oncologo.

Queste le principali caratteristiche dei pazienti: una donna di 48 anni, affetta da carcinoma della mammella metastatico in trattamento ormonale; un uomo di 58 anni, affetto da carcinoma della tiroide metastatico e da carcinoma del polmone metastatico in chemioterapia; una donna di 62 anni, affetta da carcinoma del colon trattato con chirurgia e con chemioterapia adiuvante; una donna di 53 anni, affetta da carcinoma bilaterale della mammella, operata e trattata con terapia ormonale; un uomo di 62 anni, affetto da carcinoma della vescica, operato e trattato con chemioterapia adiuvante.

Il familiare era una donna di 48 anni, vedova di un paziente deceduto a 57 anni per un carcinoma metastatico a sede primitiva non identificata.

Il gruppo si è riunito cinque volte discutendo i principali problemi. Dalle riunioni sono emersi, come maggiormente sentiti, i seguenti temi: la comunicazione della diagnosi e l'informazione, il coinvolgimento della famiglia, il tempo trascorso tra i primi sintomi della malattia e l'inizio degli accertamenti (tempo diagnostico) e quello trascorso tra la diagnosi e l'inizio della terapia (tempo terapeutico), il contatto del paziente con altri malati affetti da cancro.

I due questionari

Terminata la fase preliminare delle riunioni e discussioni, il gruppo ha preparato due questionari, entrambi con il contributo largamente prevalente dei malati che hanno proposto le domande ritenute più attinenti. Nella riunione finale i questionari sono stati giudicati esaurienti, di semplice comprensione, e di facile compilazione.

Il primo questionario, quello da compilare al momento della diagnosi, era composto da 39 domande rivolte ai seguenti temi: la comunicazione e l'informazione, le relazioni con il personale sanitario, le reazioni psicologiche, la richiesta di supporto psicologico, i tempi diagnostico e terapeutico, le relazioni con gli altri malati, le ricadute sociali, lavorative, familiari. Si trattava per lo più di domande a risposta predefinita da scegliere fra 2-3 risposte possibili; alcune domande richiedevano di quantificare un dato (ad esempio il livello della fiducia riposto nella terapia), con un punteggio compreso tra 1 (livello minimo) e 10 (livello massimo).

Il secondo questionario, quello da compilare dopo 3-6 mesi, era composto da 17 domande sui medesimi temi esplorati nel primo, ad eccezione dei tempi.

La distribuzione dei questionari

Dal 1 ottobre 2000 al 1 aprile 2001 sono stati distribuiti 189 primi questionari. Essi, previo consenso del malato, sono stati consegnati in maniera consecutiva ad ogni paziente ritenuto capace di rispondere autonomamente e di cui si prevedeva un follow-up di almeno sei mesi (per consentire la successiva consegna del secondo questionario). La consegna avveniva in occasione della seconda o della terza visita, quindi in genere 2-4 settimane dopo il primo colloquio, durante il quale il malato era stato informato della diagnosi e delle prospettive prognostiche e terapeutiche. La compilazione del questionario era anonima e la sua restituzione avveniva in busta chiusa in un apposito contenitore collocato nella sala d'attesa dell'UO. Dal 1° febbraio 2001 al 1° luglio 2001, con le medesime modalità, sono stati distribuiti 70 secondi questionari.

La valutazione dei risultati dei due questionari

I dati dei questionari sono stati raccolti in una serie di tabelle che, singolarmente, sono state valutate e discusse da un gruppo composto da un medico, due infermiere, due psicologhe. Ciascun membro del gruppo esprimeva la propria opinione in merito al risultato di ogni domanda. Al termine è stata raccolta una sintesi delle diverse opinioni, sintesi che viene presentata in questo lavoro.

Risultati

Sono stati restituiti compilati 138 (73%) primi e 43 (61%) secondi questionari.

Al primo questionario hanno risposto 58 uomini e 80 donne; l'età mediana era di 61 anni. Il grado d'istruzione era il seguente:

elementare 22 %, media inferiore 31%, media superiore 26%, laurea 6%, non precisato 15%. L'attività lavorativa era la seguente: pensionato 39%, casalinga 23%, lavoratore 27%, studente 1%, non precisata 10%.

Al secondo questionario hanno risposto14 maschi e 29 femmine; l'età mediana era di 59 anni. L'attività lavorativa era la seguente: pensionato 33%, casalinga 21%, lavoratore 32%, non precisata 14%.

La comunicazione

La prima comunicazione della diagnosi di tumore è stata fatta nel 76% dei casi da un medico ospedaliero (di area chirurgica nel 43%, oncologo nel 33%), e nel 15% dal medico di base.

Nel primo questionario il 66% dei pazienti ha giudicato completa l'informazione, ma un'elevata percentuale di malati (28%) non ha fornito risposta a questa domanda. Nel secondo questionario le rispettive percentuali sono state 49% e 42%.

Riguardo la qualità dell'informazione, elevata è risultata la percentuale di malati (84%) che ha ritenuto appropriato e garbato il modo in cui essa è stata fornita, modo che solo nel 5% dei casi è stato giudicato brusco, nell'11% distaccato.

All'inizio della malattia il 72% dei malati ha desiderato che venisse informata anche la famiglia, mentre il 22% ha preferito che l'informazione non venisse estesa ad altre persone.

Come prevedibile, la grande maggioranza dei malati ha voluto informare anche il medico curante (94%).

Mentre prima della diagnosi della propria malattia meno della metà dei malati (44%) era documentata sulle malattie oncologiche, successivamente il 73% di loro si è documentato, per lo più con il medico curante (42%). Altre fonti di informazione sono state la stampa (23%) e Internet (22%).

Le relazioni con il personale sanitario

Nel primo questionario la disponibilità al colloquio è stata giudicata buona in un'elevata percentuale di casi sia per quanto riguarda i medici (94%) che le infermiere (94%); nel secondo è emerso un certo calo per i medici (90%), un incremento per le infermiere (100%).

Molto buona sia nei confronti dei medici che delle infermiere (anche se lievemente maggiore nei riguardi delle seconde - punteggio di 9,1/10 - rispetto ai primi - punteggio 8,9/10) la libertà di esprimere i propri problemi.

Le azioni che hanno maggiormente rassicurato i malati sono state la disponibilità (36%) e la professionalità (30%), quelle che li hanno maggiormente infastiditi, peraltro in una quota di malati molto bassa, sono state la freddezza (5%) e la superficialità (4%).

Le reazioni psicologiche

Le prime reazioni alla diagnosi di tumore si sono distribuite in modo uniforme tra la paura/angoscia (20%), la rassegnazione/accettazione (23%), l'atteggiamento di lotta contro la malattia (22%), la fiducia nella medicina (28%).

Durante il trattamento il 40% dei pazienti ha segnalato di nutrire un sentimento di fiducia (livello 8,44) nel primo questionario, percentuale che si è mantenuta al 42% nel secondo (livello 8,74). Però, percentuali piuttosto elevate hanno provato sentimenti di insofferenza ("non vedo l'ora che finisca" nel 30%), oppure di tensione - paura - ansia (23%).

Al quesito sulla necessità di un supporto psicologico inizialmente il 21% ha risposto positivamente, successivamente solo il 14%.

Le altre risorse

Il 35% dei malati era informato sulle varie forme di assistenza di cui avrebbe potuto usufruire (volontariato, ADI - assistenza domiciliare integrata, trasporti gratuiti, ecc.) e sui diritti in campo lavorativo, e solo il 5% ha usufruito dell'aiuto di qualche associazione di volontariato sia all'inizio della malattia che successivamente.

I tempi

Il tempo diagnostico è stato giudicato breve o abbastanza breve nel 77% dei casi, lungo nel 20%; il tempo terapeutico è stato giudicato breve o abbastanza breve nel 92% dei casi, lungo nel 6%.

Le relazioni con gli altri malati

Una buona parte di malati (67%) ha tratto conforto dal contatto con altre persone affette da patologia tumorale, ma una percentuale non trascurabile ha gradito la solitudine durante il trattamento (33%). Nel secondo questionario la percentuale di malati che ha gradito la compagnia di altri pazienti è scesa al 57%.

Le ricadute sociali, lavorative, familiari

Già in una fase precoce di malattia il 69% dei malati ha riferito un cambiamento, di varia entità, nelle relazioni sociali con conoscenti e amici (molto nel 9%, abbastanza nel 30%, poco nel 30%).

Sin dall'inizio il 59% ha modificato la propria attività lavorativa (inclusa l'attività domestica) nella misura di 6,2/10; successivamente l'attività è stata modificata nel 72% dei casi, nella misura di 5,7/10.

All'inizio il 27% dei familiari, nella misura di 5,7/10, ha dovuto assentarsi dal lavoro per assistere il proprio congiunto, in seguito il 21%, nella misura di 4,6/10. Nel secondo questionario l'88% dei malati ha sentito i familiari più vicini rispetto al periodo precedente la malattia, il 63% ha riferito un colloquio costante o frequente con i familiari rispetto la malattia, il 28% un colloquio occasionale.

Infine, l'86% dei malati ha ritenuto di poter contare sull'aiuto di altre persone.

Nella Tabella 1 sono riportati, per confronto, i dati relativi ad alcune domande presenti nei due questionari.

Discussione

Le prime due fasi dello studio, la costituzione del gruppo di studio misto e la preparazione dei due questionari, sono state fondamentali, perché hanno consentito di entrare nelle tematiche relative all'approccio globale al malato oncologico più con lo spirito del malato, che aveva già vissuto in prima persona i problemi e le difficoltà che si volevano valutare, che con quello dell'opera-

Tabella 1 - Confronto tra primo e secondo questionario

	Primo questionario (%)	Secondo questionario (%)
Comunicazione sulla diagnosi		
Completa	66	49
Risposta non data	28	42
Buone relazioni con il personale sanitario		
Medici	94	90
Infermiere	94	100
Richiesta di supporto psicologico	21	14
Supporto dal volontariato	5	5
Gradimento della compagnia di altri malati	67	57
Modifica dell'attività lavorativa		
Paziente	59	72
Familiari	27	21

tore sanitario. Quindi il gruppo ha prodotto un questionario che, oltre ad essere di semplice comprensione e di rapida compilazione, era anche, a nostro avviso, strettamente attinente ai temi affrontati.

A conferma di ciò abbiamo raggiunto un buon tasso di adesione alla ricerca, con la compilazione del 73% dei primi e del 61% dei secondi questionari. In effetti, se è ipotizzabile che ciò sia stato favorito dalla selezione dei pazienti e dallo stretto rapporto che abitualmente si instaura tra i malati oncologici e la struttura che li segue, è anche probabile che vi abbiano contribuito le stesse caratteristiche del questionario, sentito "proprio" e strettamente attinente al recente vissuto, oltre che di compilazione non solo semplice ma anche coinvolgente.

Interessante osservare come la comunicazione della diagnosi di tumore, fatta per lo più in ambito ospedaliero, riguarda diversi reparti tra cui, in primo luogo, quelli chirurgici. Proprio nei reparti chirurgici, infatti, il malato oncologico viene più frequentemente sottoposto al primo approccio diagnostico e/o alla prima terapia. Considerata la molteplicità delle sedi di informazione, per evitare di fornire notizie contraddittorie (fonte di disagio e di sfiducia per il malato), appare importante un'uniformità di comportamento da parte dei medici dei diversi reparti. Nella nostra esperienza la costante discussione interdisciplinare dei casi si è rivelata positiva in quanto ha permesso non solo di giungere ad una condivisione della pianificazione diagnostico/terapeutica, ma anche ad un'uniformità sui modi e sui temi della comunicazione. Probabilmente le dimensioni piccolo/medie della struttura hanno favorito l'instaurarsi di un ambiente familiare ed hanno facilitato gli scambi comunicativi tra medici, malato, famiglia, e tra i diversi reparti dell'ospedale.

In effetti, i dati dello studio sono positivi riguardo i rapporti relazionali tra i pazienti e le diverse figure professionali. Il differente andamento del giudizio sulla disponibilità (che complessivamente rimane altamente positivo) osservato nei due questionari, con un calo del giudizio positivo nei confronti dei medici (da 94 a 90%) ed un incremento per le infermiere (da 94 a 100%), è esplicativo del legame molto stretto che si crea, col progredire della malattia, tra malato e personale infermieristico, mentre il medico, specie di fronte ad una malattia che peggiora e che non risente più beneficio dalla terapia antitumorale, può perdere, se non è incline all'approccio globale, il suo ruolo fondamentale e non essere più in grado di soddisfare appieno le richieste del malato. I risultati di questo studio sottolineano anche il fatto che il malato apprezza in maniera simile la disponibilità del personale sanitario e la sua competenza professionale; la disponibilità umana e la competenza professionale non vanno, in altre parole, mai disgiunte.

Una nota non positiva riguarda la completezza dell'informazione, con elevate percentuali di mancate risposte sia nel primo che nel secondo questionario. Tali percentuali potrebbero essere legate ad una formulazione non corretta del quesito, oppure al fatto che i malati non avevano ancora, al momento di compilare il questionario, un termine di paragone con il quale confrontare la completezza dell'informazione, ma potrebbero anche essere sintomatiche di una comunicazione inadeguata. Comunque, il tema della comunicazione richiede un approfondimento.

Sin dal momento della diagnosi è apparsa rilevante la necessità da parte del paziente di coinvolgere i familiari; infatti, nel difficile percorso di adattamento psicologico alla malattia, non è risultata quasi mai esclusa la famiglia che, per mantenere il suo fondamentale ruolo di sostegno, dovrà a sua volta essere sostenuta. Nella nostra esperienza la maggior parte dei malati ha contato su di un forte sostegno familiare, traendo la sensazione di una famiglia molto vicina, pronta ad un dialogo continuo proprio sui temi della malattia, e disposta ad un forte impegno, anche a scapito della propria attività lavorativa.

Difficile interpretare, a causa della dispersione delle reazioni, il dato della reazione alla diagnosi, e probabilmente improprio attribuire ad esso una valenza positiva o negativa. Comunque, almeno la metà dei malati ha assunto sin dall'inizio un atteggiamento di lotta contro la malattia, confermato dal fatto che il 73% di essi ha cercato (in vario modo) di approfondire le proprie informazioni. In definitiva, emerge, anche se non in maniera predominante, la figura di un paziente attivo che vuol essere protagonista nelle scelte che lo riguardano. Fiduciosa nella terapia si è dimostrata una percentuale di malati discretamente elevata sia all'inizio (40%) che successivamente (42%); di converso, però, queste percentuali esprimono anche i dubbi, le paure, le inquietudini che interessano una buona metà dei malati.

Colpisce altresì la percentuale molto bassa di malati che, sia in un primo momento (quello della comunicazione della diagnosi) come in un momento successivo (quello delle terapie e dei controlli), ha espresso la necessità di usufruire di un supporto psicologico. Il dato sorprende in tutti i sensi. Sarebbe infatti logico attendersi che entrambi i momenti, quello dell'adattamento alla diagnosi ed alle nuove prospettive di vita e quello dei problemi connessi con la terapia e con i controlli, siano momenti di grande richiesta di sostegno.

Più di una considerazione giustifica questo atteggiamento inaspettato. La prima, forse semplicistica ma verosimile per la nostra piccola realtà, riguarda le relazioni molto favorevoli tra i pazienti e gli operatori sanitari, per cui gli stessi operatori, con la loro aperta disponibilità al dialogo, offrono un efficace sostegno psicologico; risalta, al proposito, l'altissimo gradimento nei confronti delle infermiere. In secondo luogo la maggior parte dei malati sente di poter contare su di un robusto sostegno sia da parte della famiglia (elevata è stata infatti la percentuale di malati che ha coinvolto la famiglia nella comunicazione della diagnosi, ed elevata è anche la percentuale di malati che ha sentito la famiglia vicina e pienamente disposta al sostegno) che da parte della cerchia delle

proprie conoscenze. Quindi, relazioni familiari e sociali molto positive, accanto ad una riservatezza connaturata nella popolazione del nostro territorio, possono spiegare il fatto che i malati si siano sentiti già sufficientemente supportati e non abbiano richiesto altri interventi sanitari che non fossero quelli dedicati espressamente alla cura.

In realtà, come l'esperienza puntualmente insegna, con il procedere della malattia, i problemi psicologici, specie nei casi ad evoluzione sfavorevole, crescono, ed emerge, sia nel malato che nella famiglia, quel fabbisogno di sostegno che inizialmente era stato ritenuto superfluo. Allora, l'iniziale presunzione di essere in grado di fronteggiare tutte le ricadute della malattia cade e lascia il posto ad una situazione di disagio in un momento ben più problematico di quello iniziale. Pertanto, nell'ottica di un approccio globale e con uno sguardo rivolto ai bisogni futuri, è opportuno offrire al malato il sostegno psicologico sin dall'inizio, sfruttando i modi e i tempi che lo rendono maggiormente accetto. Uno strumento valido potrebbe essere il colloquio congiunto con la presenza simultanea dell'oncologo e della psicologa in occasione della prima visita, allo scopo di presentare l'intervento sanitario e quello psicologico come parti indissolubili di un unico piano di cura.

Come già detto, oltre alla famiglia la maggioranza dei malati ha ritenuto di poter contare su di un aiuto esterno appartenente alla propria sfera sociale, ritenuta evidentemente molto disponibile al sostegno. Al contrario, carente è risultata l'informazione sulla possibilità di fruire di interventi di sostegno da parte del volontariato e dell'assistenza sociale. Per migliorare questa situazione, e per giungere al pieno utilizzo di tutte le risorse disponibili in campo oncologico (alcune delle quali sotto-utilizzate proprio perché poco conosciute), la strada preferibile è rappresentata dalla costruzione di un'adeguata "rete" relazionale che integri, oltre alla cerchia familiare ed extrafamiliare, anche le varie forme di volontariato e di assistenza sociale.

La sensazione del tempo che passa è emersa, dal preliminare lavoro di gruppo, come un elemento di grande rilievo per il malato. Certamente, di fronte alla certezza od al semplice sospetto di una diagnosi così grave, tutto il tempo deve essere impiegato utilmente, sottoponendo tempestivamente il malato alle indagini necessarie ed alla terapia adeguata; nell'espletamento dell'iter diagnostico e terapeutico sono assolutamente da evitare le lungaggini, i ritardi, le inefficienze.

Nel nostro studio entrambi gli intervalli di tempo considerati (quello diagnostico e quello terapeutico) sono stati giudicati soddisfacentemente brevi. Da rilevare come il tempo terapeutico dipenda esclusivamente dall'assetto organizzativo sanitario ospedaliero, che appare efficiente. Il tempo diagnostico, invece, dipende anche da altri fattori come, ad esempio, il ritardo con cui il malato si presenta dal proprio medico, ed appare migliorabile sia sensibilizzando la popolazione ad un più sollecito ricorso al proprio curante al manifestarsi dei primi sintomi della malattia, che potenziando l'efficienza dei servizi diagnostici ambulatoriali.

Le relazioni che si instaurano tra i malati sono importanti. Basti pensare al confronto di esperienze che ricorre nei dialoghi della sala d'attesa o delle sale d'infusione, confronto che talora può rassicurare, come nel caso del malato che percorre una strada già percorsa con successo da altri, talaltra può turbare, come nel vissuto sfavorevole di un "compagno di viaggio" perso strada facendo e che ad un certo momento non è più presente, come d'abitudine, agli appuntamenti.

I nostri malati si sono distribuiti in modo uniforme tra quelli che gradivano la compagnia di altri malati, tra quelli che preferivano rimanere da soli, e tra quelli che desideravano stare con i familiari. Anche di queste preferenze si può tenere conto, per cui, disponendo di una struttura adatta e flessibile e conoscendo le singole preferenze, è possibile collocare il malato durante le sedute di chemioterapia nella situazione che gli è più congeniale.

Interessante osservare come la percentuale di casi che gradiva la compagnia di altri malati è scesa dal 67% del primo questionario al 57% del secondo. Una giustificazione di tale calo potrebbe risiedere per alcuni malati nell'aggravamento della malattia che induce ad una maggior riservatezza, per altri nel vissuto di altri casi ad evoluzione sfavorevole, vissuto che porta ad evitare altri confronti forieri di sensazioni spiacevoli.

Come prevedibile, sin dall'inizio l'impatto della malattia sulle abitudini lavorative dei malati e, in misura minore, delle famiglie è stato pesante. Considerato che per lo studio abbiamo selezionato i malati con aspettativa di vita di almeno sei mesi e che fossero in grado di rispondere autonomamente, escludendo di fatto i malati più gravi e quelli più anziani, il dato, riferito a tutta la casistica, è sottostimato per cui le ripercussioni lavorative, familiari e sociali sono in realtà ancora maggiori. Si tratta di una situazione che va tenuta in debito conto e per la quale, operando nell'ottica di un approccio globale al malato, è necessario ricercare ed attivare le necessarie risorse sociali da integrare con quelle sanitarie, per consentire ai malati ed alle famiglie di affrontare serenamente tutti i gravi problemi che li assillano.

Conclusioni

Da questo studio, che analizza in modo semplice e preciso la nostra realtà in quanto frutto della fondamentale esperienza dei malati e dei familiari, e che alle volte conferma, altre volte contraddice, le nostre precedenti impressioni, sono emerse indicazioni molto utili per avviare una serie di iniziative atte a costruire una rete operativa capace di coprire meglio le esigenze dei nostri malati e delle loro famiglie. La prima sarà quella di integrare le diverse risorse sanitarie, ospedaliere e territoriali, con il volontariato ed il sociale. La seconda quella di inserire in maniera più incisiva l'attività di sostegno psicologico. La terza quella di adeguare la collocazione del malato in seno all'UO in base alle personali preferenze.

Appendice

Concludendo questo lavoro voglio ricordare tre persone che hanno fornito il loro prezioso contributo e che non sono più tra noi. Ricordo Donato per avermi insegnato ad assaporare, quando ormai la malattia l'aveva costretto immobile nel letto e mai più l'avrebbe potuta gustare, la delicata fragranza delle foglie del sommacco in primavera, fragranza che ogni anno ritorna puntuale tra le mie mani. Ricordo Maria per la serenità ingenua, quasi fanciullesca, per l'ottimismo di tutti i momenti, anche di quelli più difficili, e per la saldezza dei legami familiari che l'hanno sempre confortata. Infine, ricordo Eligio per la tenacia e la consapevolezza di scelte combattive, per lo spirito polemico, mai domo, e per la grande speranza, viva anche quando la fine era prossima ed i successi si facevano sempre più piccoli e sempre più rari.

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Master in telededattica applicata alla medicina

A master on distant learning and telemedicine

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Riassunto

Gli Autori definiscono i presupposti delle applicazioni telematiche nelle moderne tecnologie didattiche della medicina e della chirurgia. Esse si concretizzano nella telededattica o didattica da postazioni remote, che comunque non sostituisce, bensì integra, le metodiche di didattica cosiddetta tradizionale. Gli Autori illustrano modalità, metodiche di espletamento ed obiettivi di un master di II livello in telededattica applicata alla medicina, che verrà attivato nel prossimo anno accademico in undici facoltà mediche italiane sotto il coordinamento della II Facoltà di Medicina e Chirurgia dell'Università degli Studi di Roma "La Sapienza". Tale master è destinato ai docenti delle facoltà mediche ed agli operatori del servizio sanitario nazionale. Gli obiettivi che il master persegue sono inerenti l'acquisizione del linguaggio multimediale per la telededattica in ambito medico e l'integrazione opportuna con i modelli tradizionali di insegnamento, nonchè la completa acquisizione degli strumenti telematici per una loro sapiente applicazione alle scienze mediche e quindi alla telemedicina, al teletriage ed alla telechirurgia. Eur. J. Oncol., 8 (3), 211-213, 2003

Parole chiave: **didattica remota, teletutoraggio, telemedicina**

Summary

The Authors define the bases of telededactic applications in modern teaching technologies in the field of Medicine and Surgery. They are carried out by distant learning, which however does not substitute, but rather completes the methods of so-called traditional learning. The Authors present the modalities, the methods of accoplishment and the objectives of a II level Master in distant learning applied to Medicine, which will start in the next academical year in 11 Italian Schools of Medicine, under the direction of the II Schools of Medicine and Surgery of the University of Rome "La Sapienza". This Master is intended for the teachers of the Medical Schools and the operators of the national health service. The aims of the Master are those of learning a multimedial language for telededactics in medicine and its appropriate integration in the traditional teaching methods, as well as the complete acquisition of telematic instruments for a proper application in medical sciences and therefore in telemedicine, teletriage and telesurgery. Eur. J. Oncol., 8 (3), 211-213, 2003

Key words: **distant learning, telementoring, telemedicine**

Introduzione

La telematica studia sistemi complessi capaci di autogoverno per la realizzazione di obiettivi attraverso l'elaborazione delle informazioni, la loro conversione in forme idonee ai canali di collegamento disponibili e la loro trasmissione.

Ciò permette il trasferimento di dati, figure, azioni, filmati, elaborazioni grafiche e suoni attraverso l'interazione di elaboratori elettronici e sistemi di telecomunicazione.

La telededattica, mediante l'utilizzo di infrastrutture hardware e software per la creazione di un sistema bidirezionale interattivo di comunicazione/informazione, consente un insegnamento/apprendimento da postazioni remote (formazione a distanza) che

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non presuppone la presenza di docenti e studenti nello stesso luogo.

La formazione a distanza applicata alla medicina ed alla chirurgia non si pone quindi in alternativa alla didattica formale in un'aula universitaria o professionalizzante in una corsia o in una sala operatoria, bensì la integra, offrendo nuove opportunità a docenti e studenti.

Il "docente telematico" deve soddisfare gli obblighi istituzionali che la Didattica di discipline medico-chirurgiche impone, incentrando però sempre più la propria attenzione non tanto sull'insegnamento quanto sull'apprendimento, inteso come percorso per acquisire un ruolo professionale[1].

Materiali e metodi

Molte e complesse sono le problematiche che si aprono nell'istruire cicli di formazione a distanza in ambito medico-chirurgico, ma quella più pressante riguarda sicuramente la formazione dei docenti.

Sensibile a queste problematiche, il MIUR (Ministero per la Istruzione, la Università e la Ricerca Scientifica), ha istituito in 11 facoltà mediche italiane, distribuite in tutto il territorio nazionale, un master di II livello, unico nel suo genere, in teledidattica applicata alla medicina, sotto il coordinamento della II Facoltà di Medicina e Chirurgia dell'Università degli Studi di Roma "La Sapienza".

Le facoltà mediche interessate, oltre alla II Facoltà di Medicina e Chirurgia dell'Università degli Studi di Roma "La Sapienza", sono quelle delle Università di Novara-Piemonte Orientale, Milano, Genova, Pisa, Ferrara, Ancona, Napoli-II Università, Bari, Catanzaro e Catania.

Molteplici sono i settori disciplinari interessati nella formazione, perché questa si possa espletare in maniera quanto più esauriente possibile, e vanno dalle scienze mediche, alla ingegneria delle telecomunicazioni, alla informatica, alla pedagogia, alla psico-sociologia, al diritto, alla economia aziendale, senza peraltro trascurare coloro ai quali è destinato il master, ovvero i docenti universitari e gli operatori del Servizio Sanitario Nazionale.

Il master avrà una durata complessiva di due anni di corso per la maturazione di 120 crediti formativi, di cui almeno 40 di tipo professionalizzante, prevederà l'organizzazione di programmi didattici comuni ed ambienti didattici condivisi tra le varie sedi con postazioni telematiche individuali per ogni discente e, al termine del corso provvederà al rilascio di una certificazione che legalmente riconosca i Crediti acquisiti.

Le metodiche su cui si basa la teledidattica sono di quattro tipi:

– il teleseminario,
– la videoconferenza,
– la televalutazione,
– la biblioteca informatica multimediale.

Obiettivi e risultati attesi

Gli obiettivi che il master persegue sono inerenti l'acquisizione del linguaggio multimediale per la teledidattica in ambito medico e l'integrazione opportuna con i modelli tradizionali di insegnamento, nonchè la completa acquisizione degli strumenti telematici per una loro sapiente applicazione alle scienze mediche e quindi alla telemedicina, al teletriage ed alla telechirurgia.

Discussione

Dialogare per via telematica senza poter vedere chi apprende, saper ascoltare attraverso un elaboratore per capire e soddisfare le esigenze degli studenti, saper valutare l'efficacia dei programmi di teledidattica attraverso tests di valutazione quanto più asettici possibile, presuppone essenzialmente l'acquisizione di due ordini di valori: acquisire il linguaggio multimediale informatico in modo da poter gestire le informazioni senza correre il rischio di banalizzare i contenuti, e saper effettuare una adeguata scelta delle informazioni per la individuazione dei percorsi più idonei al raggiungimento degli obiettivi didattici curriculari irrinunciabili, caratterizzanti o professionalizzanti prefissati.

Il linguaggio multimediale simbolico di alto livello di tipo interattivo pone le sue basi nelle parole e nei numeri scritti, letti o ascoltati, ma supportati da suoni, immagini ed animazioni, regolati da norme di tipo tecnico che non ne limitano fantasia ed efficacia ma anzi ne favoriscono ordine e sistematicità.

Circa la scelta e la tipologia delle informazioni, sono essenzialmente cinque i punti da considerare: sorgente, qualità e quantità, metodi di trasmissione, destinazione e tempi necessari. Andrà quindi valutata l'efficacia sull'utente attraverso una documentata modifica del comportamento[2].

Il teleseminario ripercorre cicli di lezioni formali, ma con metodologia tale da favorire l'apprendimento autonomo, ed a tal fine utilizza la strutturazione di ipertesti multimediali, che consentono la possibilità di navigare nel contesto dell'offerta formativa attraverso tutte le possibili interconnessioni tra le diverse sezioni del testo, per ricercare il percorso più idoneo al raggiungimento degli obiettivi prefissati.

Essi facilitano la capacità di interpretazione delle informazioni, inducono ad una semplice memorizzazione dei dati, conducono con rapidità al collegamento mentale tra concetti, eventi ed azioni e si adattano a qualsiasi percorso cognitivo, come in particolare il *problem-based* ed il *problem-solving learning*.

Viene tuttavia persa l'ottica speculativa del "sapere strutturato" propria di un trattato a tutto vantaggio del "sapere investigativo" basato sulla ricerca attiva da parte del discente[2].

La videoconferenza permette un dibattito a distanza tra due o più interlocutori ponendo le basi per il tutoraggio virtuale (*telementoring*) e consentendo la formulazione di *"second opinion"* in telemedicina, *teletriage* e telechirurgia.

In ambito chirurgico il *telementoring* è considerato oggigiorno un metodo educativo aggiuntivo, ma ovviamente non esclusivo, per la formazione e l'addestramento chirurgico, consentendo altresì lo svolgimento di *training* chirurgici in ambienti virtuali ricostruiti al computer.

Tale metodo può riguardare l'insegnamento di una tecnica o di una procedura chirurgica da parte di uno specialista verso un chirurgo in formazione a distanza, o può essere utilizzata per l'insegnamento di una nuova tecnica chirurgica da parte di uno specialista verso un collega già formato ma con minore esperienza[1, 3, 4].

Lo specialista ha il compito di seguire, assistere e guidare l'allievo in tempo reale, ma non è in grado di intervenire direttamente fin quando saranno perfezionati e quindi applicabili sistemi in grado di consentire il controllo remoto di un braccio robotico.

Obiettivo principale sarà dunque quello di trasmettere informazioni verbali motivate da parte del docente che verranno tradotte in azioni controllate da parte del discente[1, 3, 4].

Restano problemi ancora aperti e controversi la valutazione dei progressi nell'apprendimento per via telematica, l'autenticazione e la certificazione dei risultati ottenuti e la programmazione di eventuali percorsi di recupero. Da ultimo, un utile ausilio alla formazione a distanza risiede nelle biblioteche informatiche multimediali, che devono consentire una semplice fruibilità di banche dati anche da postazioni remote domiciliari.

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Quarantunesimo caso di mesotelioma tra gli operai del Compartimento di Bologna delle Ferrovie dello Stato

Forty-first case of mesothelioma among the workers at the Bologna Department of the Italian State Railroads

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Riassunto

Viene riportato il quarantunesimo caso di mesotelioma (40 mesoteliomi pleurici e 1 pleuro-peritoneale) in un lavoratore professionalmente esposto ad asbesto nel Compartimento di Bologna delle Ferrovie dello Stato (FS). Eur. J. Oncol., 8 (3), 215-219, 2003

***Parole chiave*: asbesto, mesotelioma pleurico, ferrovie italiane**

Summary

This report refers to the forty-first case of mesothelioma (40 pleural mesotheliomas and 1 pleuro-peritoneal mesothelioma) arisen in a worker occupationally exposed to asbestos at the Bologna Department of the Italian State Railroads (Ferrovie dello Stato = FS). Eur. J. Oncol., 8 (3), 215-219, 2003

***Key words*: asbestos, pleural mesothelioma, Italian railroads**

Introduzione

A partire dagli anni '30 -'40, l'asbesto è stato impiegato nelle ferrovie di molti Paesi.

In Italia, fin dagli anni '40, l'asbesto è stato utilizzato per isolare caldaie e tubature. Negli anni '60 è stato impiegato per coibentare la cabina di guida di un particolare modello di locomotore. Dagli anni '50 -'60 l'asbesto è stato largamente utilizzato per coibentare i rotabili di nuova costruzione e per sostituire i materiali isolanti infiammabili (come il sughero) in carrozze di vecchia costruzione.

A causa dell'utilizzo dell'asbesto nei rotabili ferroviari sono stati esposti, ed in parte lo sono ancora, alle fibre del minerale: 1) i lavoratori addetti alla costruzione, manutenzione, riparazione, decoibentazione e demolizione dei rotabili; 2) i lavoratori che operano in ambienti di lavoro inquinati da asbesto, compreso il personale viaggiante; 3) la popolazione residente vicino alle linee ferroviarie o a fabbriche ove i rotabili vengono prodotti o riparati o decoibentati o demoliti; 4) i familiari dei lavoratori esposti; 5) la popolazione residente vicino a binari "morti" sui quali sono parcheggiati vagoni dismessi usati come contenitori di scorie contenenti asbesto; e 6) i viaggiatori, e fra questi soprattutto i pendolari.

Da circa 20 anni il Centro di Ricerche Epidemiologiche della Fondazione Europea di Oncologia e Scienze Ambientali "B. Ramazzini" sta raccogliendo un'ampia casistica italiana di tumori, in particolare mesoteliomi, correlabili all'esposizione all'asbesto usato nelle ferrovie. Nell'ultimo resoconto[1] i casi di mesoteliomi da noi raccolti erano 199. A tutt'oggi i casi di mesoteliomi che fanno parte della nostra casistica sono 207, dei quali 186 mesoteliomi pleurici, 1 pericardico, 9 peritoneali, 1 pleuro-peritoneale e 10 a sede non altrimenti specificata.

Il numero di casi di mesotelioma da asbesto usato nelle ferrovie insorti in operai delle Ferrovie dello Stato (FS) della sede compartimentale di Bologna ammonta a 41 (Tabella 1). Fra questi è compreso il caso che qui presentiamo.

Resoconto del caso

T.M., nato il 29/9/1923 in provincia di Bologna, già residente nella stessa provincia, ed ivi deceduto il 17/1/2001.

Ex-fumatore.

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Tabella 1 - Mesoteliomi tra lavoratori della sede compartimentale di Bologna delle FS

N.	Caso	Sesso	Periodo lavorativo	Mansione	Sede del mesotelioma	Latenza[a] (anni)	Sopravvivenza[b] (mesi)	Età alla morte (anni)	Anno di morte
1	C.F.[2]	M	1954-1976	Collaudatore, elettricista	Pleura	28	29	53	1984
2	C.W.[2]	M	1940-1974	Manutentore	Pleura	18	44	64	1979
3	F.G.[2]	M	1965-1968	Pannellista, macchinista[c]	Pleura	17	17	46	1985
4	G.G.[2]	M	1953-1976	Lamieraio	Pleura	33	11[d]	51[d]	1987[d]
5	O.L.[e][2]	M	1945-1970	Lamieraio, aggiustatore	Pleura	38	7	68	1983
6	S.P. [2]	M	1954-1961	Elettricista[f]	Pleura	27	22	48	1983
7	S.R.[2]	M	1973-1983	Verniciatore[g]	Pleura	12	21	43	1984
8	V.S.[3]	M	1956-1985	Pannellista, verificatore	Pleura	29	22[d]	54[d]	1987[d]
9	Z.A.[4]	M	1949-1979	Conduttore macchine utensili	Pleura	38	8[d]	66[d]	1988[d]
10	D.E.[5]	M	1955-1987	Elettromeccanico	Pleura	32	11[d]	54[d]	1988[d]
11	B.O.[6]	M	1942-1977	Elettromeccanico	Pleura	43	22	61	1987
12	S.L.[7]	M	1962-1966	Elettricista[h]	Pleura	26	6	62	1988
13	B.L.[e][8]	M	1971-1988	Motorista	Pleura	16	13	38	1988
14	P.W.[9]	M	1947-1973	Elettricista	Pleura	32	30	60	1981
15	B.N. [10]	M	1944-1967	Manovale e deviatore[i]	Pleura	37	3	67	1982
16	C.F.[11]	M	1957-1987	Falegname, manutentore	Pleura	32	14[d]	64[d]	1990[d]
17	M.S. [11]	M	1963-1983	Manutentore	Pleura	26	22[d]	51[d]	1991[d]
18	A.G.[12]	M	1943-1977	Elettricista, aggiustatore	Pleura	47	6	63	1990
19	C.M.[13]	M	1954-1978	Lamieraio, macchinista[l]	Pleura	37	5	67	1991
20	P.G.[13]	M	1954-1977	Pannellista, aggiustatore	Pleura	36	16	71	1991
21	M.E.[14]	M	1942-1980	Aggiustatore meccanico	Pleura	49	4	67	1991
22	G.P.[15]	M	1952-1988	Usciere, portinaio	Pleura	40	10[d]	62[d]	1993[d]
23	G.G.[16]	M	1945-1977	Manovratore, deviatore	Pleura	47	3	73	1992
24	G.V.[16]	M	1957-1988	Falegname, caporeparto	Pleura	35	12[d]	65[d]	1993[d]
25	C.D.M.W.[17]	M	1949-1965	Elettromeccanico, impiegato	Pleura	43	16[d]	64[d]	1993[d]
26	B.F.[18]	M	1949-1984	Elettricista	Pleura-peritoneo	40	13	63	1990
27	B.V.[19]	M	1945-1967	Verniciatore	Pleura	44	13	72	1990
28	U.T.[20]	M	1962-1988	Lamieraio	Pleura	29	24	60	1993
29	T.E.[21]	M	1949-1977	Verniciatore[m]	Pleura	43	11	66	1993
30	B.M.[22]	M	1972-1990	Falegname	Pleura	21	27[d]	56[d]	1995[d]
31	A.M.[23]	M	1960-1986	Tappezziere, collaudatore	Pleura	34	2	58	1994
32	D.D.[24]	M	1944-1971	Manutentore[n]	Pleura	45	44	77	1993
33	L.M.[25]	M	1945-1969	Magazziniere, commesso	Pleura	49	–[o]	–[o]	–[o]
34	D.E.U. [26]	M	1943-1983	Manutentore	Pleura	51	13	68	1995
35	C.C.[27]	M	1949-1967	Verniciatore	Pleura	46	–[o]	–[o]	–[o]
36	L.G.[28]	M	1960-1989	Manutentore	Pleura	34	–[o]	–[o]	–[o]
37	G.G.[29]	M	1956-1991	Operaio	Pleura	35	15	65	1996
38	S.A.[29]	M	1976-1992	Elettricista[p]	Pleura	16	–[o]	–[o]	–[o]
39	L.R.	M	1975-1987	Macchinista, falegname	Pleura	23	–[o]	–[o]	–[o]
40	N.S.[q]	M	?-?	Operaio di armamento	Pleura	–	–	–[r]	1986
41	T.M.[s]	M	1941-1972	Elettricista	Pleura	58	23	77	2001
Media						**34,7[t]**	**16,0[u]**	**61,3[u]**	

[a] Tempo intercorso tra l'inizio dell'esposizione e la comparsa dei primi sintomi e segni della neoplasia
[b] Tempo intercorso tra l'inizio della sintomatologia ed il decesso
[c] Dal 1968 al 1971 ha lavorato come aggiustatore meccanico presso il Deposito Locomotive di Mestre (VE) e quindi, dal 1971 al 1983, ha lavorato come macchinista
[d] Dato acquisito successivamente alla pubblicazione del caso
[e] Ha lavorato presso le OGR delle FS di Rimini
[f] Dal 1961 al 1981 ha lavorato, sempre come elettricista, presso il Deposito Locomotive di Trieste
[g] Dal 1971 al 1973 ha lavorato come falegname presso le OGR delle FS di Rimini
[h] Dal 1942 al 1961 ha lavorato con varie mansioni presso le sedi delle FS di Trieste, Campobasso e Udine; dal 1967 al 1988 ha lavorato come capotecnico elettricista presso il Deposito Locomotive di Udine
[i] L'attività professionale è stata svolta anche, in periodi non precisati, presso il Compartimento FS di Ferrara e nella sede di Roccapalustre in Sicilia
[l] Nel periodo in esame ha lavorato anche presso il Compartimento FS di Genova
[m] Dal 1977 dipendente del Dopolavoro Ferroviario con la mansione di responsabile della manutenzione degli edifici
[n] Nel 1931 ha lavorato come addetto all'inventario presso l'Officina Casaralta di Bologna (produce rotabili ferroviari)
[o] Vivente al momento dell'ultimo follow-up
[p] Nel 1963 ha lavorato come manovale presso l'Officina Casaralta di Bologna (produce rotabili ferroviari)
[q] Per questo caso non è noto il periodo lavorativo. Il lavoratore era impiegato presso la sede di Piacenza del Compartimento FS di Bologna
[r] Per questo caso non è nota la data di nascita
[s] Caso oggetto della presente pubblicazione
[t] Calcolata su 40 dei 41 casi (1 caso senza dati circa il periodo lavorativo)
[u] Calcolata su 35 dei 41 casi (1 lavoratore senza dati circa il periodo lavorativo e senza data di nascita, 5 lavoratori viventi alla data dell'ultimo follow-up)

Anamnesi lavorativa

– 1941-1972: ha lavorato presso le Officine Grandi Riparazioni (OGR) di Bologna, svolgendo la mansione di elettricista addetto alla manutenzione e riparazione di rotabili ferroviari. Durante lo svolgimento della sua attività lavorativa è stato esposto ad asbesto impiegato come materiale di coibentazione delle parti elettriche.
– 1972: in pensione.

Storia clinica

– 1979: ipertensione arteriosa.
– 1985: gammapatia monoclonale.
- Febbraio 1999: il paziente lamenta la comparsa di tosse produttiva persistente.
- 12/2/1999: 1° Ricovero in regime di Day-Hospital nella Divisione di Pneumologia.
  – ECG: "Tracciato normale".
  – Rx torace: "Accentuazione della trama a carattere vascolare. Non alterazioni pleuro-parenchimali in atto. Ombra cardiaca e piccolo circolo nei limiti".
  – Diagnosi di dimissione: "Sindrome bronchitica subacuta protratta in paziente con gammapatia monoclonale".
– Giugno 2000: il paziente lamenta dispnea ingravescente e presenza di versamento pleurico a sn.
– 4/7/2000: 2° Ricovero in regime di Day-Hospital nella Divisione di Pneumologia.
  – ECG: "Tracciato normale".
  – Si esegue toracentesi ecoguidata a sn con fuoriuscita di 2.500 cc di liquido pleurico.
  – Esame citologico di citocentrifugato di liquido pleurico: "Reperto citologico sospetto per neoplasia maligna a possibile origine mesoteliale". La successiva revisione dei preparati, eseguita da uno degli autori, ha confermato la diagnosi.
  – Esame istologico di citoincluso di liquido pleurico: "Il citoincluso allestito da un coagulo è caratterizzato da numerosi aggregati di elementi epiteliomorfi aventi nucleo ingrandito ed irregolare fornito di nucleolo prominente ed abbondante rima citoplasmatica. Detti elementi risultano: calretinina +/-; citocheratine AE1-AE3+; CK7+; CK20-; CK19+; CK ad alto peso molecolare +; S100-; HMB45-; antigene epatocitario -. Il reperto risulta fortemente sospetto per neoplasia maligna a possibile origine mesoteliale" (fig. 1).
  – Broncoscopia: "Trachea normale, carena in asse. A sn i rami segmentari del bronco lobare inferiore sono lievemente ovalizzati per compressione estriseca senza segni di infiltrazione della mucosa. Si esegue broncolavaggio per ricerche citologiche in tale territorio. Gli altri distretti bronchiali e l'emisistema di ds, esplorati fino ai rami subsegmentari, non presentano alterazioni".
  – Esame citologico di liquido di broncolavaggio bronco sn: "Negativa la ricerca di cellule neoplastiche".
  – TC torace: "Presenza di cospicuo versamento pleurico a sn con raccolte saccate evidenti già al terzo superiore in sede apicale, latero-posteriormente, ed a livello della pleura pericardica. La somministrazione di mezzo di contrasto non mette in evidenza a livello del cavo pleurico alterazioni focali significative (utile controllo citologico e/o pleuroscopico). Non si evidenziano significativi aumenti dimensionali delle linfoghiandole mediastiniche né delle surrenali".
– 22/7/2000-26/7/2000: 1° Ricovero ospedaliero in Divisione di Pneumologia.
  – ECG: "Tracciato normale".
  – Rx torace: "Versamento pleurico basale sn che risale lungo la scissura. Controlateralmente non si apprezzano alterazioni pleuro-parenchimali con caratteristiche di attività. Ombra cardiaca e piccolo circolo nei limiti".
  – Si esegue toracentesi con fuoriuscita di 500 cc di liquido pleurico sieroematico.
  – Esame citologico di citocentrifugato di liquido pleurico: "Negativa la ricerca di cellule neoplastiche".
  – Esame istologico di citoincluso di liquido pleurico: "Il citoincluso allestito da un coagulo è caratterizzato da leucociti (prevalentemente linfociti) e da rari aggregati di elementi mesoteliali iperplastici. Negativa è la ricerca di cellule neoplastiche".
  – Diagnosi di dimissione: "Tumore maligno della pleura parietale. Si trasferisce il paziente in altra sede per essere sottoposto a pleuroscopia e biopsia pleurica ed eventuali procedimenti chirurgici".
– 26/7/2000-12/8/2000: 2° Ricovero ospedaliero in Divisione di Pneumotisiologia.
  – ECG: "Tachicardia sinusale (104/min), con alterazioni della ripolarizzazione tipo T appiattite in sede infero-laterale".
  – Si esegue toracoscopia con biopsie pleuriche a sn e talcaggio pleurico.
  – Esame istologico di biopsie della pleura: "Mesotelioma maligno epiteliale, ben differenziato, infiltrante la fascia toracica". Secondo la classificazione del Panel Nazionale dei Mesoteliomi[30], si tratta di un mesotelioma epiteliomorfo con aspetto solido (prevalente) e bifasico (in aree limitate) (figs. 2, 3).
  – Rx torace: "Persistenza del versamento pleurico basale sn. Non segni di pneumotorace".
  – Consulenza chirurgica: "Il quadro non risulta suscettibile di trattamento chirurgico".
  – Consulenza oncologica: "Si ritiene opportuno eseguire un trattamento citotossico palliativo con cisplatino e gemcitabina".
  – Diagnosi di dimissione: "Mesotelioma pleurico".
- 30/8/2000: Si esegue 1° ciclo di chemioterapia per via sistemica con cisplatino e gemcitabina.
– 11/10/2000: Rx torace: "Riduzione del volume del campo polmonare sn con marcato ispessimento della limitante pleurica diffuso e mammellonato, velamento della base e rinforzo del disegno broncovasale. Modesto rinforzo del disegno anche a ds. Ombra cardiaca sostanzialmente nei limiti. Aorta apparentemente lievemente prominente all'arco".

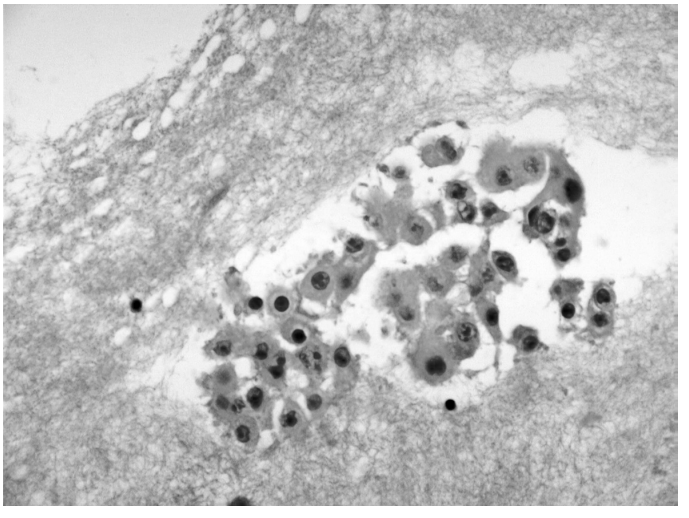

Fig. 1. Citoincluso. Cellule neoplastiche sospette per mesotelioma epiteliomorfo. E.E. x 400

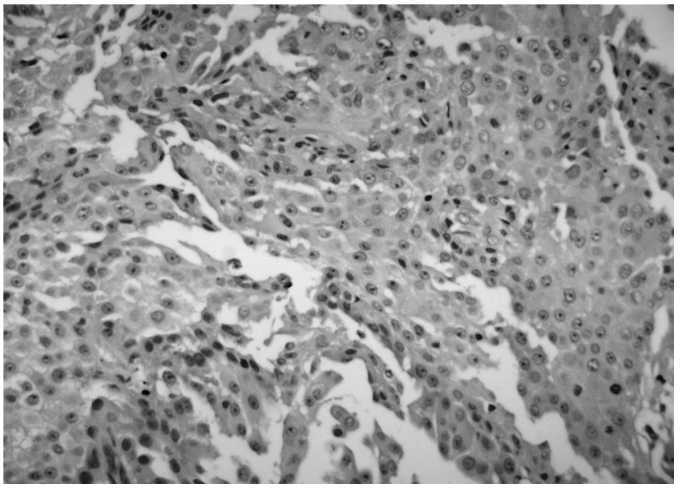

Fig. 2. Biopsia pleurica. Mesotelioma epiteliomorfo: area con aspetto solido. E.E. x 100

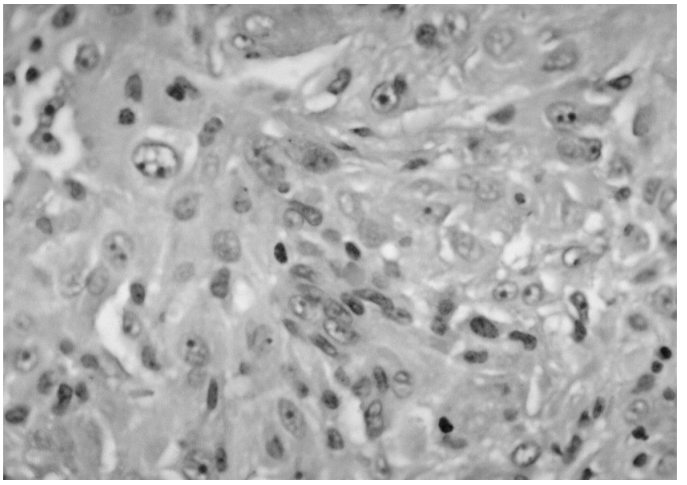

Fig. 3. Biopsia pleurica. Mesotelioma epiteliomorfo: area con aspetto prevalentemente solido. E.E. x 400

  - Rx rachide dorso-lombare: "Rachide discretamente in asse con moderata scoliosi lombare sn convessa. Segni artrosici diffusi sia a livello somatico sia a livello delle articolazioni inter-apofisarie posteriori e spazi intersomatici modestamente asimmetrici, ridotti a livello di L4-L5 e di L5-S1. Il tono calcico è diffusamente ridotto. Non si rilevano crolli somatici, ma alcuni corpi vertebrali nel tratto medio-dorsale sono lievemente ridotti di altezza, come pure il corpo di D12. È appena apprezzabile un nucleo calcifico di aspetto litiasico, di circa 1 cm di diametro, che si proietta sul territorio dell'ombra renale sn".
- 16/10/2000: Si esegue 2° ciclo di chemioterapia per via sistemica con cisplatino e gemcitabina. Il trattamento è stato mal tollerato e quindi sospeso per la comparsa di effetti collaterali di notevole entità.
- 7/11/2000: Rx torace: "Presenza di discreto ispessimento a carattere produttivo, di aspetto mammellonato con versamento pleurico dell'intero campo polmonare di sn. Nulla da segnalare a ds. Ombra cardiaca nei limiti. Segni di aortosclerosi".
- Dicembre 2000: Il paziente lamenta un aggravamento della dispnea, astenia, toracalgia e comparsa di epistassi.
- 30/12/2000-4/1/2001: 3° Ricovero ospedaliero in Divisione di Medicina.
  - Rx torace: "Esteso opacamento dell'emitorace di sn con aspetti di ipodiafania. Note di accentuazione della trama broncovasale al polmone ds senza altre significative alterazioni pleuro-parenchimali. Verosimile marcata ectasia del bulbo aortico".
  - Ecografia addome superiore: "Ecostruttura epatica omogenea, priva di lesioni a carattere focale, con margini lisci, regolari. Colecisti distesa, priva di calcoli. Vie biliari principali e vena porta di calibro regolare. Nulla a carico di milza, reni, surreni e pancreas. Presenza di versamento pleurico a sn, organizzato".
  - Diagnosi di dimissione: "Mesotelioma pleurico".
- 17/1/2001: Decesso. Diagnosi di morte: "Mesotelioma pleurico". Tempo intercorso tra la comparsa dei primi sintomi e segni della neoplasia ed il decesso: 24 mesi. Età al decesso: 77 anni.

Conclusioni

I lavoratori delle OGR delle FS sono esposti ad asbesto nell'esercizio delle loro mansioni specifiche e/o in quanto hanno operato, qualunque sia stata la loro mansione, in ambienti notoriamente inquinati da fibre del minerale.

Essi pertanto sono a rischio di sviluppare mesotelioma, come dimostra la nostra casistica che comprende un gran numero di casi di mesotelioma insorti in lavoratori delle OGR delle FS.

Il lavoratore oggetto di questo resoconto è stato sicuramente esposto ad asbesto. La durata dell'esposizione (32 anni), ed il tempo di latenza (periodo intercorso tra l'inizio dell'esposizione e la comparsa dei primi sintomi e segni della neoplasia) (58 anni) sono compatibili con l'origine professionale della neoplasia.

Il caso di mesotelioma pleurico qui descritto va quindi correlato all'esposizione ad asbesto avvenuta nell'espletamento dell'attività lavorativa.

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Eur. J. Oncol., vol. 8, n. 3, pp. 221-224, 2003

Recurrent aggressive fibromatosis of the suvraclavicular fossa: long-term response with chemotherapy. A case report

Fibromatosi aggressiva recidiva della fossa sovraclaveare: risposta a lungo termine con chemioterapia. Resoconto di un caso

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Summary

Aggressive fibromatoses are rare neoplasms originating from fascial and aponeurotic tissues. These tumours have a locally aggressive behaviour, infiltrating the surrounding structures and the neuro-vascular bundles, with consequent pain and functional deficit. Surgery is the treatment of choice, but high local relapse rates, from 39% to 79% of cases, are reported. Radiotherapy, used either as primary therapy or as an adjuvant to surgery, gives good results in terms of local control of the disease, avoiding major cosmetic and functional sequelae. Systemic therapy is usually reserved for recurrences of aggressive fibromatosis after surgery and radiotherapy, but up to now there are not widely accepted protocols. The Authors report their experience with a case of aggressive fibromatosis of the suvraclavicular fossa, recurring after surgery and adjuvant radiotherapy, which has been successfully treated with polychemotherapy. Eur. J. Oncol., 8 (3), 221-224, 2003

***Key words*: aggressive fibromatosis, neoplastic local recurrence, surgery, polychemotherapy**

Riassunto

Le fibromatosi aggressive sono neoplasie rare che prendono origine dai tessuti fasciali ed aponeurotici. Questi tumori hanno un comportamento localmente aggressivo, infiltrando le strutture ed i fasci vascolo-nervosi circostanti con conseguenti dolore e deficit funzionali. La chirurgia è il trattamento di scelta, ma è gravata da un'alta percentuale di recidive locali, oscillanti tra il 39% ed il 79%. La radioterapia, impiegata sia come trattamento primario che come terapia adiuvante, dà buoni risultati in termini di controllo locale della malattia, evitando sequele funzionali ed estetiche importanti. La terapia sistemica viene generalmente riservata alle recidive della fibromatosi aggressiva dopo chirurgia e radioterapia, ma attualmente non esistono ancora protocolli universalmente accettati. In questo lavoro riportiamo la nostra esperienza di un caso di fibromatosi aggressiva della regione sovraclaveare, che aveva recidivato dopo trattamento chirurgico e radioterapico adiuvante ed è stata trattata con successo con polichemioterapia. Eur. J. Oncol., 8 (3), 221-224, 2003

***Parole chiave*: fibromatosi aggressiva, recidiva locale neoplastica, chirurgia, polichemioterapia**

Introduction

Aggressive fibromatoses, also called desmoid tumours, are rare, slow-growing and histologically benign neoplasms, which originate from fascial, muscular and aponeurotic tissues[1]. These tumours have a locally aggressive behaviour, invading surrounding tissues, particularly the adjacent neuro-vascular structures, with consequent pain and functional deficit; in the case of intra-abdominal or intra-thoracic extension, the invasion of vital organs can lead to death[1, 2].

Surgery is the treatment of choice for these tumours, and a disease-free margin seems to reduce the local relapse rate, which is particularly high and ranges from 39%[3] to 79%[4] in surgical series. However, expecially for intra-abdominal and extra-adbominal proximal localizations, radical surgery would result in mutilations

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and severe dysfunction, and radiotherapy, used either alone or as adjuvant to conservative surgery, offers good local control without major cosmetic and functional sequelae[5].

Systemic therapy is usually reserved for recurrences of aggressive fibromatosis after surgery and radiation, but it is not standardized, as no large series of patients treated with cytotoxic or non-cytotoxic therapies are reported in the literature[6].

We report our experience with a case of aggressive fibromatosis of the suvraclavicular fossa, recurring after surgery and adjuvant radiotherapy, which has been successfully treated with combination cytotoxic therapy; furthermore the different therapeutic options are discussed.

Case report

A 23 year old man presented with an asymptomatic 5 cm suvraclavicular mass, which had appeared 5 months before; no history of previous trauma was referred. Cytology on fine needle aspiration had not been conclusive for diagnosis.

The patient underwent surgical biopsy: after incision of the skin, a large mass was found, strictly adherent to the internal jugular vein and the scalene and trapezius muscles, which extended inferiorly into the superior thoracic outlet, contracting adherences with the subclavear vessels and, medially, with the brachial plexus, without invading the pleura. An incisional biopsy detected aggressive fibromatosis, with invasion of muscolar tissue. A CT scan (fig. 1a) confirmed the extension of the tumour from the suvraclavicular fossa, along the subscapular muscle and behind the neurovascular bundle, down to a level corresponding to the 6th dursal vertebra. Staging of disease was completed with an abdominal CT scan and a colonoscopy, which excluded intra-abdominal localizations and correlations with a Gardner's sindrome.

On this basis, debulking surgery was performed: through a suvraclavear incision the tumour was excised, leaving small residual areas along the neurovascular subclavear bundle, the internal jugular vein and, inferiorly, the periostium of the first rib and intercostal muscle.

Given the incomplete surgical resection, the patient received adjuvant radiotherapy on tumour bed, with a total dose of 50 Gy.

Two years later, a CT scan showed a local relapse of the disease, localized between the subscapular muscle and the thoracic wall. The patient was asymptomatic and simple observation was considered. A new CT scan (fig. 1b), one year after, showed further local progression of the disease and the patient complained of pain.

For these reasons, the patient underwent a systemic cytotoxic therapy, with a weekly low dose regimen including methotrexate, 30 mg/m^2 and vinblastine, 6 mg/m^2, for 5 months, obtaining a substantial reduction of tumour mass at CT restaging at the end of treatment (fig. 1c), with complete resolution of algic symptoms. Such clinical and radiological response (fig. 1d) has mantained and the patient is presently alive and symptom-free after 8 years of follow-up.

Discussion

Desmoid tumours are rare, accounting for 0.03% of all cancers and 3% of soft tissue tumours[7]; for this reason, large series and trials are lacking and uncertainties on treatment still exist.

In spite of its benign histological appearance, aggressive fibromatosis has a locally invasive behaviour and the invasion of neuro-vascular structures leads to severe impairment and dysfunction; involvement of vital structures from intra-abdominal or intra-thoracic localizations may sometimes cause death[1, 2]. The therapeutic approach is controversial as the natural history of these tumours has not been completely understood.

Surgical resection is considered by most authors the primary modality of treatment[1, 4, 8], but high relapse rates are reported; aggregate recurrence rates from the literature range from 52% for cases with free margins of resection, to 81% for cases with residual tumour after surgery[9]. Moreover, the importance of the margins of resection is not clearly estabilished, as its influence on local control rates has been emphasized by some authors[2, 8, 10], but not confirmed by others[1, 11], who have reported low rates of local relapse even in the presence of positive margins. Such results may be partly explained by the small numbers of patients in the reported series, not homogeneous regarding sites of fibromatosis (intra- or extra-abdominal) and including either primary lesions or recurrences. However, stable disease in patients followed with observation only has been reported in 88% of 68 cases[4], and anecdotal descriptions of spontaneous regression are described in several studies.

The rôle of radiation therapy, both in the adjuvant and the primary setting, is debated. Good results have been reported with radiotherapy alone in the treatment of aggressive fibromatosis, with a 78% local control rate in patients who presented unfavourable factors, such as larger tumours, infiltration of neuro-vascular structures or tumours considered not resectable[5]. Adjuvant radiation in patients with inadequate or incomplete margins of resection seems to reduce the risk of local failure[2, 9], with an aggregate rate of local control of 77% in series from the literature.

In our patient, surgical resection could not achieve local radicality, because of the infiltration of important neuro-vascular structures, and treatment was then completed with subsequent adjuvant radiotherapy. Total radiation dose on the tumour bed was 50 Gy, consistent to indications in the literature, indicating an optimal dose of 50-60 Gy[5].

At two years of follow-up, the patient presented a local relapse, which had a relatively rapid and symptomatic progression, indicating an aggressive behaviour of the tumour. Even if no estabilished prognostic factor for an aggressive behaviour is reported in the literature, the suvraclavicular fossa has been described as one of the sites of aggressive fibromatosis resistant to cure[4] and age younger than 30 has been reported by some authors as a risk factor[9].

Systemic therapy with cytotoxic drugs was then considered, in order to avoid a secondary resection which would have resulted in important complications and would probabily not have obtained a sufficient radicality.

The rarity of desmoid tumours has not allowed the conduction of large clinical trials, and data on systemic therapy derive from small series, usually including cases of recurrence after surgery and radiotherapy, when a resective approach is not possible or would result in major complications. Several cytotoxic and non-cytotoxic agents have been employed. Favourable responses have been obtained with the administration of antioestrogen agents, particularly tamoxifen[12], with an antitumour effect which seems independent of the expression of hormone receptors[6]. Non-steroidal anti-inflammatory drugs have sometimes induced the regression of desmoid tumours, expecially in the case of intra-abdominal localizations, and the antidesmoid activity seems related to cyclooxygenase inhibiton[12].

More numerous series are reported with the use of cytotoxic agents. The combination of dacarbazine and doxorubicin, based on a conventional sarcoma chemotherapy, gave objective responses in 6 out of 9 evaluable patients in the original study[13], and this efficacy has been confirmed in other experiences. The weekly vinblastine-methotrexate combination is the most frequently utilized regimen, because of its low toxicity profile and proven ef-

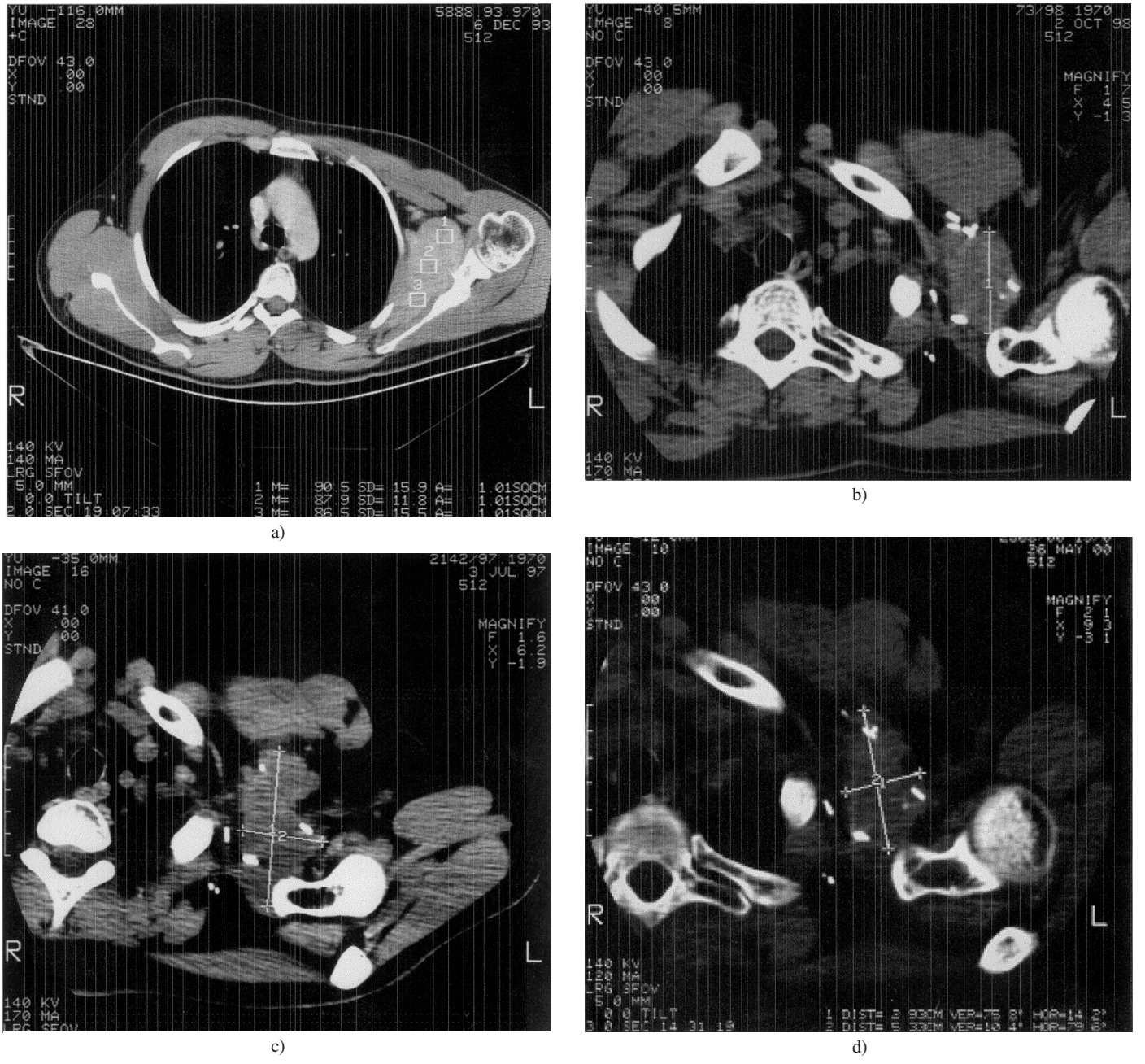

Fig. 1. CT scans of suvraclavicular fossa. **1a** (upper left): primary lesion; **1b** (upper right): local relapse after surgery and radiotherapy; **1c** (lower left): tumour reduction after chemotherapy; **1d** (lower right): no relapse at follow-up

ficacy: in the largest series reported in the literature[14], an obiective response lasting more than 5 years was obtained in 21 out of 24 patients treated, and two of three relapsing patients responded to re-treatment. This regimen was used in our patient, who received 22 cycles of chemotherapy, without major toxicities, obtaining a clinical response with resolution of pain, which is mantained after 8 years of follow-up.

Conclusions

Aggressive fibromatoses are tumours with an unpredictable, even if usually slow, growth and tendency to local invasion; data from the literature indicate that their aggressiveness must not be underestimated: "desmoid is a benign tumour, not a benign disease"[2].

Surgery is the approach of choice, and the achievement of negative resection margins is the goal, even if residual disease does not necessarily affect the survival rates. Radiotherapy should be considered as an adjuvant to surgery in the case of margin-positive tumours, or as an alternative when the resection of the tumour would result in severe complications.

In the case of recurrences after primary treatment, surgery is reported to be effective[2]; when surgical resection is not feasible, radiotherapy is an effective alternative[9].

Systemic therapies represent salvage treatments in those patients relapsing after surgery or radiotherapy, but large trials are

lacking because of the rarity of this disease and the limited indications to chemotherapy. The weekly vinblastine-methotrexate regimen has a low toxicity profile and a good efficacy, and can represent an important option in those cases where the anatomical location and the particularly aggressive behaviour of the fibromatosis makes local therapies not sufficient.

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Laparoscopic segmentary ureterectomy for low-grade, low-stage transitional cell carcinoma

Ureterectomia segmentaria laparoscopica per carcinoma a cellule di transizione di basso grado e stadio

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Summary

***Aim*. A case of laparoscopic segmentary ureterectomy for low-grade, low-stage transitional cell carcinoma (TCC) of the mid-distal ureter is described. *Patient and methods*. An open umbilical access was used (Hasson technique), with 3 additional ports in the right inferior hemi-abdomen. Segmentary ureteral resection was accomplished using diathermy and the ureteral continuity was restored by laparoscopic freehand suturing with intracorporeal knotting technique. *Results*. Operating time was 220 minutes and length of hospital stay was 3 days. The intravenous pyelogram after the removal of JJ stent at 6 weeks showed a patent anastomosis without extravasation or signs of tumour recurrence. *Conclusions*. For unifocal, low-stage and low-grade upper urinary tract TCC, laparoscopic resection of the ureter may prove satisfactory as a minimally invasive alternative to open surgery, with excellent local control of the disease. Eur. J. Oncol., 8 (3), 225-227, 2003**

***Key words*: laparoscopy, transitional cell carcinoma, ureter, upper urinary tract**

Riassunto

***Finalità*. Viene presentato un caso clinico di ureterectomia segmentaria (tratto medio-distale) laparoscopica per carcinoma a cellule di transizione (TCC) di basso grado e stadio. *Paziente e metodi*. Si è utilizzato l'accesso ombelicale di Hasson con 3 porte aggiuntive disposte nell'emiaddome inferiore destro. È stata eseguita, per via laparoscopica, una resezione segmentaria del tratto ureterale, con ansa diatermica, con successiva anastomosi uretero-ureterale mediante sutura con la tecnica del nodo interno. *Risultati*. La durata dell'intervento è stata di 220 minuti, con 3 giorni di degenza. L'urografia eseguita dopo rimozione dello stent JJ a 6 settimane dall'intervento non ha mostrato soluzioni di continuo parietali nè segni di recidiva locale di malattia. *Conclusioni*. Si può affermare che l'approccio laparoscopico nei TCC unifocali a basso grado e stadio delle vie urinarie alte rappresenta un'alternativa soddisfacente e minimamente invasiva alla chirurgia a cielo aperto, con un eccellente controllo locale della malattia. Eur. J. Oncol., 8 (3), 225-227, 2003**

***Parole chiave*: laparoscopia, carcinoma a cellule di transizione, uretere, tratto urinario superiore**

Introduction

Transitional cell carcinoma (TCC) of the upper urinary tract is relatively uncommon (less than 5% of all TCCs). Standard treatment for patients with upper tract urinary TCC and a normal contralateral renal unit is nephroureterectomy with excision of a bladder cuff: this has traditionally been accomplished by open surgery and, more recently, by various laparoscopic techniques[1, 2]. In selected patients with a solitary kidney and/or low-grade (G1-G2), low-stage (Ta-T1) tumours, endourological management has recently come to be regarded as an acceptable way of treatment with a high cure rate[1, 3]. However, a large tumour volume or a difficult ureteral anatomy may in many cases preclude endourological management. In these circumstances, segmentary ureterectomy is an accepted option, with a low morbidity and encouraging long-term results[1].

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To our knowledge, there is little experience with laparoscopic conservative surgery for upper urinary tract TCC. A case of laparoscopic segmentary ureterectomy for TCC of the mid-distal ureter is described.

Case report

A 55-year-old white male patient came to our observation for gross haematuria and pain in the right flank. His previous medical history was unremarkable and no chemical and/or environmental risk factors were present. Ultrasound examination of the urinary tract showed grade 1 hydronephrosis on the right side, with normal contralateral kidney and bladder. Intravenous pyelography demonstrated a 2.5 cm filling defect in the right iliac ureter (fig. 1), confirmed by subsequent retrograde pyelography; at ureteroscopy a large papillary tumour of the ureter was seen, and the entire ipsilateral renal unit inspected for associated lesions. The histological examination of biopsies showed grade 1-2 TCC of the ureter. The preoperative abdomino-pelvic CT scan showed no signs of ureteral wall involvement and/or periureteral fat infiltration. No enlarged lymphnodes were detected, and routine diagnostic work-up was negative for metastatic disease. Therefore, the tumour was categorized as stage T1, and deemed amenable to conservative surgery.

Ureteroscopic treatment was discarded, due to the bulky volume of the lesion. Therefore, laparoscopic resection was undertaken. After retrograde passage of a stent up to the right ureter, pneumoperitoneum was established by open umbilical access following the Hasson tecnique. Thereafter, 3 additional 12 mm ports were positioned in the right lower abdomen. The tumour-bearing right iliac ureter was identified, dissected free and mobilized 2 cm above and below the level of the lesion. Segmentary ureteral resection was accomplished using diathermy. The specimen was extracted from the abdomen in a standard laparoscopic sac and inspected; biopsies of the surgical margins were taken and sent for frozen section pathologic examination. There were no signs of infiltration. The ureteral continuity was restored by direct, end-to-end anastomosis of the spatulated ureteral stumps, with interrupted 4-0 poliglycolic acid sutures and intracorporeal knotting technique. Complete haemostasis was obtained, and the abdomen deflated. The ports were inspected and a drainage tube was left in place. Duration of the procedure was 220 minutes. Definitive pathological examination confirmed TCC of the ureter without signs of infiltration of the ureteral wall and with negative surgical margins (pT1, G2) (fig. 2). The postoperative course was uneventful. The drainage tube was removed the day after surgery and the patient was discharged on postoperative day 3. The JJ stent was removed 6 weeks after surgery, under local anaesthesia, and an intravenous pyelogram was performed, demonstrating a good visualization of the anastomosed right ureter and no signs of tumour recurrence (fig. 3).

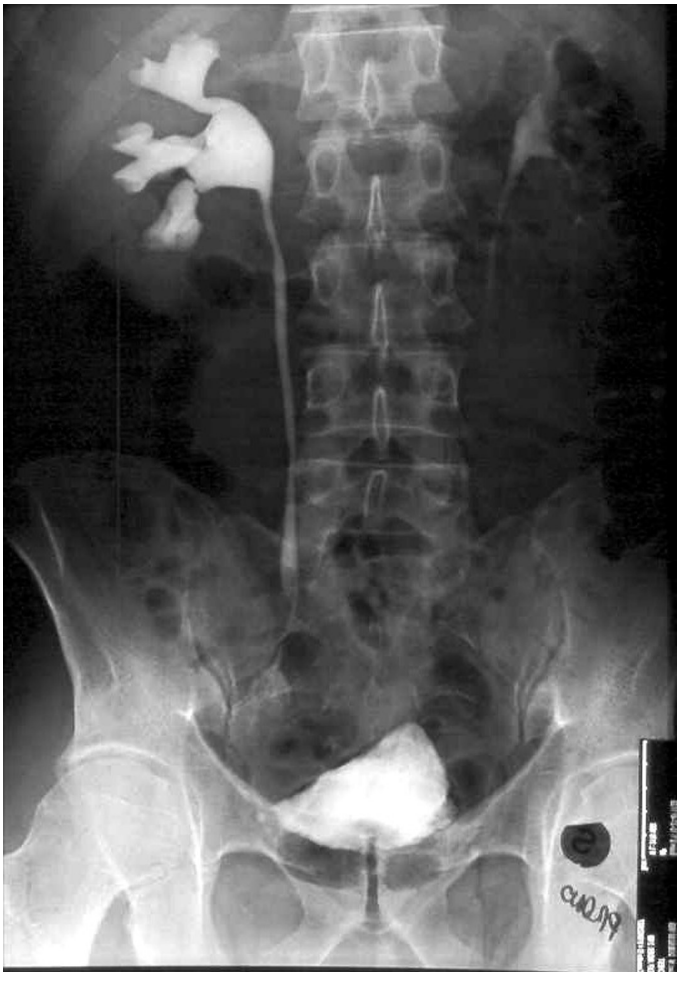

Fig. 1. Intravenous pyelography demonstrated a 2.5 cm filling defect in the right iliac ureter

Discussion

Upper urinary TCC is an aggressive tumour with a tendency to high grade disease, multifocality, local recurrence and distant metastases. The 5-year survival following radical nephroureterectomy depends on pathological stage, which is 91% for stage Tis, Ta or T1 and 43% for stage T2 tumours [4-7]. Local extension outside the renal pelvis or ureter into renal parenchyma, peripelvic/ureteric fat, perihilar tissue (T3 or T4) or lymph nodes (N1 or N2), is present in 30% of patients at presentation. The 5 –year survival rate in these cases is only 10% to 23%, irrespective of treatment modality. Probability of local and/or distant tumour recurrence also correlates with primary tumour stage: at 2 years, it is 60% for T3 disease and 70% for T4 disease, respectively[3, 4]. The progression rates for Ta and T1 stages are 6% and 21%, respectively[3]. Because a 30% to 60% local recurrence rate can be expected in the residual ureteral urothelium, complete distal ureterectomy with excision of a bladder cuff is the accepted gold standard treatment for TCC of the renal pelvis and ureter[2]. However, the outcome of treatment modalities depends mostly on tumour pathology. Grade 1 TCC, which is almost always superficial without *lamina propria* invasion (stage Ta), has a low recurrence

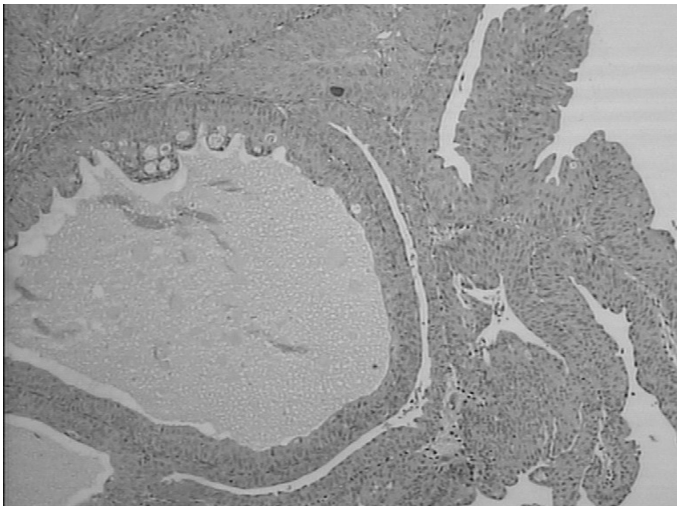

Fig. 2: Histopathological examination: transitional cell carcinoma of ureter (T1 G2)

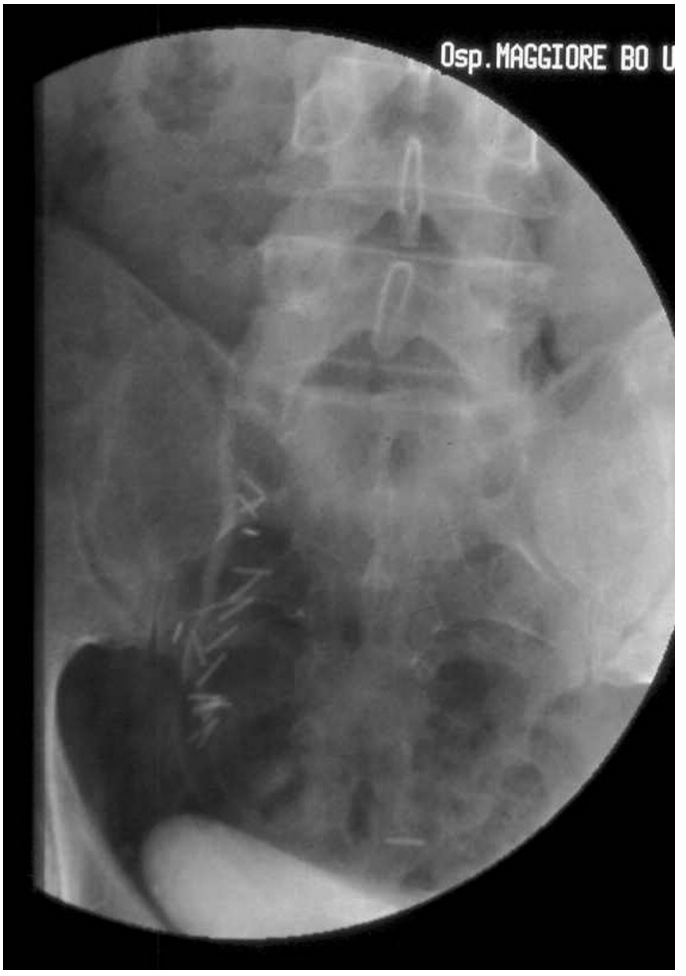

Fig. 3: Intravenous pyelogram showed a good visualization of the anastomosis of the right ureter and no signs of tumour recurrence.

rate and, more importantly, it rarely progresses to muscle invasive and/or metastatic disease. These tumours have an excellent outcome also when treated conservatively. In contrast, grade 3 TCC has an invasive character and significant metastatic potential. These cases have a poor prognosis regardless of the surgical approach. Grade 2 urothelial tumours have a more variable behaviour. The high ipsilateral tumour recurrence rate after open conservative surgery has led to the suggestion that grade 2 upper tract TCC may benefit mostly from radical nephroureterectomy[1, 3, 6, 8].

In the case presented, laparoscopic treatment was carried out providing adequate tumour resection with no complications.

Conclusion

Conservative management of ureteral malignancy is still a challenging problem. Minimally invasive nephron-sparing strategies are justified for low-stage, low-grade unifocal disease. However, strict inclusion criteria are crucial for the outcome of surgery, and a strict surveillance protocol including ureteroscopy to detect recurrent upper tract TCC is mandatory whenever a conservative approach is contemplated. Laparoscopic resection of the ureter may prove satisfactory as a minimally invasive alternative to open surgery, with excellent cancer control.

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