EUROPEAN JOURNAL OF ONCOLOGY

GIORNALE EUROPEO DI ONCOLOGIA

Official Organ of the Italian Society of Tumours
SIT
Prevention, Diagnosis, Therapy

Organo Ufficiale della Società Italiana Tumori
SIT
Prevenzione, Diagnosi, Terapia

Associato all'Unione Stampa Periodica Italiana

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

PUBLISHER
MATTIOLI 1885 - SPA
CASA EDITRICE

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

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

EUROPEAN JOURNAL OF ONCOLOGY
GIORNALE EUROPEO DI ONCOLOGIA

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ELEVENTH COLLEGIUM RAMAZZINI STATEMENT

CALL FOR AN INTERNATIONAL BAN ON ASBESTOS: STATEMENT UPDATE

RICHIESTA DI MESSA AL BANDO INTERNAZIONALE DELL'AMIANTO: AGGIORNAMENTO DELLA POSIZIONE DEL COLLEGIUM RAMAZZINI

To eliminate the continuing burden of disease and death that is caused worldwide by exposure to asbestos, the Collegium Ramazzini calls for an immediate ban on all mining and use of asbestos. To be effective, the ban must be international in scope and must be enforced in every country in the world.

Asbestos is an occupational and environmental hazard of catastrophic proportion. Asbestos has been responsible for over 200,000 deaths in the United States, and it will cause millions more deaths worldwide. The profound tragedy of the asbestos epidemic is that all illnesses and deaths related to asbestos were entirely preventable.

Safer substitutes for asbestos exist, and they have been successfully introduced in many nations. The grave hazards of exposure to asbestos and the availability of substitute materials have led a growing number of countries to eliminate all import and use of asbestos. In the United States asbestos usage has been drastically reduced but not eliminated. By the end of 2004 national asbestos bans are scheduled to be in place in all 25 member countries of the European Union as well as Chile, Argentina, El Salvador, Uruguay, Honduras, Australia, Gabon, Seychelles, Saudi Arabia, and Kuwait. South Africa and Japan have also announced the intention to ban asbestos, and public health campaigns for asbestos bans have been under way since the 1990s in Brazil, South Korea, Vietnam and India.

The Collegium Ramazzini

The Collegium Ramazzini is an international academic society that examines critical issues in occupational and environmental medicine. The Collegium is dedicated to the prevention of disease and the promotion of health. The Collegium derives its name from Bernardino Ramazzini, the father of occupational medicine, a professor of medicine of the Universities of Modena and Padua in the late 1600s and the early 1700s. The Collegium is independent of commercial interests, comprised of some 180 physicians and scientists from 30 countries, each of whom is elected to membership.

Background

The health consequences of the use of asbestos in contemporary industrial society have been amply documented in the world scientific literature. The toll of illnesses and deaths among asbestos workers in mining, construction, and heavy industry is well known. The pioneering work of British, South African, and Italian investigators[1-3] laid the foundation for the definitive investigations by Irving Selikoff and his colleagues of insulation workers in the United States. Selikoff's monumental studies showed initially the greatly increased mortality experience of insulation workers[4], and later, the synergistic relationship between tobacco smoking and asbestos work[5]. Men who were followed more than 20 years from first onset of exposure sustained excessive risks of lung cancer and mesothelioma, as well as risks of other neoplasias[6]. These risks affected not only asbestos workers, but their families and neighbours (from material on clothing or plant emissions), users of products that contain asbestos, and the public at large[7].

Asbestos is a general term applied to naturally occurring fibrous minerals long popular for their thermal resistance, tensile strength, and acoustic insulation. Asbestos minerals are divided into two groups: serpentine and amphibole. There is only one type of serpentine asbestos, chrysotile, also known as white asbestos. It is the most commonly used form of asbestos, accounting for over 90% of worldwide use. Amphibole minerals include five asbestos species: amosite, crocidolite, tremolite, anthophyllite, and actinolite. Two of these are the most commercially valuable forms: amosite, or brown asbestos, and crocidolite, or blue asbestos. The other amphibole minerals are of lesser commercial importance.

All forms of asbestos cause asbestosis, a progressive fibrotic disease of the lungs. All can cause lung cancer, malignant mesothelioma and gastrointestinal cancers[8-10]. Asbestos has been declared a proven human carcinogen by the US Environmental Protection Agency (EPA) and by the International Agency for Research on Cancer of the World Health Organization (WHO)[9, 11]. Early indications that chrysotile might be less dangerous than other forms of asbestos have not held up[10]. The preponderance of scientific evidence to date demonstrates that chrysotile too causes cancer, including lung cancer and mesothe-

lioma[12, 13]. Canadian chrysotile that is amphibole-free still is associated with mesotheliomas[14, 15].

A leading asbestos researcher, Julian Peto and his colleagues, predict that deaths from mesothelioma among men in Western Europe will increase from just over 5,000 in 1998 to about 9,000 by the year 2018. Peto and colleagues have now further documented the expected cases in Great Britain through 2050, and expect 90,000 deaths from mesothelioma, 65,000 after 2001[16]. In Western Europe, past asbestos exposure will cause a quarter of a million deaths from mesothelioma over the next 35 years. The number of lung cancer deaths caused by asbestos is at least equal to the number of mesotheliomas, suggesting that there will be more than a half a million asbestos cancer deaths in Western Europe over the next 35 years[17]. In Sweden, Jarvholm[18] has reported that the number of deaths caused each year by malignant mesothelioma is greater than the number of deaths caused in that country by all workplace injuries. The International Labour Organization has estimated that the annual global toll from asbestos diseases is at least 100,000[19]. Leigh[20] and LaDou[21] have estimated that the eventual toll of deaths from asbestos may well reach 5-10 million, not counting additional deaths caused by continuing asbestos use. The toll in most countries still using large amounts of asbestos may never be fully recorded.

An immediate international ban on the mining and use of asbestos is necessary because the risks cannot be controlled by technology or by regulation of work practices. The strictest occupational exposure limits in the world for chrysotile asbestos (0.1 f/cc) are estimated to be associated with lifetime risks of 5/1,000 for lung cancer and 2/1,000 for asbestosis[22]. These exposure limits, while technically achievable in the United States and in a few other highly industrialized countries, still result in unacceptable residual risk. In newly industrializing countries engaged in mining, manufacturing, and construction, asbestos exposures are often much higher, and the potential for epidemics of asbestos disease is greatly increased[23, 24].

Scientists and responsible authorities in countries still allowing the use of asbestos should have no illusions that "controlled use" of asbestos may be a realistic alternative to a ban. Environmental exposure from the continued use of asbestos still is a serious problem. A recent study of women residing in communities in Canadian asbestos mining areas found a sevenfold increase in the mortality rate from pleural cancer[25]. Large quantities of asbestos remain as a legacy of past construction practices in many thousands of schools, homes, and commercial buildings in developed countries, and are now accumulating in thousands of communities in developing countries.

An international ban on mining and use of asbestos is necessary because country-by-country actions have shifted rather than eliminated the health risks of asbestos. The asbestos industry has had a powerful influence over many countries. Even in the United States, the asbestos industry succeeded in 1991 in overturning the EPA's recommended ban and phase-out of asbestos by a technical ruling in the courts. Canada, Russia, and other asbestos-exporting countries have developed major markets in newly industrializing nations. Canada, in particular, has tried to use its influence at a number of international scientific organizations by downplaying the dangers of chrysotile asbestos. It unsuccessfully brought a case to the World Trade Organization (WTO) to overturn national bans on asbestos[26]. Such industrial-sponsored attempted influence has been exerted for many years by trying to control the outcome of scientific organizations such as the WHO[27]. Conditions of current asbestos use in developing countries now resemble those that existed in the industrialized countries before the dangers of asbestos were widely recognized.

The commercial tactics of the asbestos industry are similar to those of the tobacco industry. In the absence of international sanctions, losses resulting from reduced cigarette consumption in the developed countries are offset by heavy selling to the Third World. In similar fashion, the developed world has responded to the asbestos health catastrophe with an enlightened ban on the use of asbestos. In response, the asbestos industry is progressively transferring its commercial activities and the health hazards to the Third World.

Multinational asbestos corporations present a deplorable history of international exploitation. These firms opened large and profitable internal and export markets in Brazil, elsewhere in South America, and in India,Thailand, Nigeria, Angola, Mexico, Uruguay, and Argentina. Brazil is now the fifth largest producer of asbestos in the world, after Russia, Canada, Kazakhstan, and China[28]. While asbestos use in the United States amounts to less than 20 g per person per year, asbestos use in Brazil averages more than 680 g per person per year; in Thailand the figure is 1,500 g per person per year, in Ukraine it is 1,800. *Per capita* asbestos consumption is over 2000 g annually in Russia, Kazakhstan, and Zimbabwe. In India, Kazakhstan, Zimbabwe, Algeria, and Colombia, use of asbestos has been increasing according to data through 2002[28].

About 90% of global asbestos use today is in asbestos cement construction materials, mainly flat sheet corrugated roofing panels and pipes. Installation, renovation, maintenance, and demolition of these materials gives rise to very high exposures for millions of workers and members of the general public every day all over the world[29].

By the time the issue of national asbestos bans was brought before the WTO, the only type of asbestos remaining in international commerce was chrysotile. WTO ruled in 2001 that national asbestos bans were justified because of the non-threshold cancer risk of asbestos exposure, the practical impossibility of "controlled use" of asbestos products in construction and the availability of safer substitute materials[30]. Even so, world asbestos use has levelled off at around 2 million metric tons per year over the last 5 years, and is concentrated in countries where prevention and compensation of asbestos disease are minimal.

In 2005, most asbestos products are sold by national companies, there are no longer asbestos-based multinational corporations. These companies under-price makers of safer, competitive materials by not bearing the costs of occupational and environmental illness their products are causing. These companies are a formidable threat to public health scientists who investigate asbestos hazards and seek to bring about corrective measures and raise awareness. Scientists and public officials have faced death threats and attacks on their professional career and reputations in the court and through political processes. International campaigns of support have been needed to prevent the victimization of public health workers advocating asbestos bans in Brazil and India. The corrupting influence of the asbestos interests is a worldwide threat to the goal of developing expertise and public health programmes in toxic substances control, which will be necessary to achieve more substantial economic development in every country in the new century[31].

Conclusion

Because of economic and technologic considerations, the safe use of asbestos is not practicable. With the proven availability of safer substances, there is no reason to tolerate the public health disaster arising from the production and use of asbestos. The total ban already introduced in a number of countries is spreading and should be extended worldwide.

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Eur. J. Oncol., vol. 10, n. 1, pp. 9-30, 2005

Asbestos-related disease risks still exist

I rischi delle malattie da amianto sono tuttora presenti

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Summary

While many countries have passed laws to ban all uses of asbestos, it is still widely used in the world today. New markets have been developed particularly in the developing world. The asbestos industry promotes controlled use as an acceptable public health policy for the continued use of asbestos. In addition they have promoted the use of chrysotile asbestos as the safe alternative to replace the amphibole forms of asbestos. The Collegium Ramazzini's concern for this continued use of asbestos formed the basis for the "Call for an Internation Ban on Asbestos" in 1999. In order to update the knowledge base for recommending this ban, the Collegium Ramazzini is issuing an Update Statement on the health risks from exposure to asbestos (XI Collegium Ramazzini Statement). Eur. J. Oncol., 10 (1), 9-30, 2005

Key words: **asbestos, disease risk, ban**

Riassunto

Anche se molti paesi hanno promulgato leggi per mettere al bando tutti gli usi dell'amianto, questo minerale è ancora oggi largamente usato nel mondo. Sono stati avviati nuovi mercati, soprattutto nei paesi in via di sviluppo. L'industria dell'amianto promuove un uso controllato, come provvedimento accettabile di sanità pubblica, per continuare il suo utilizzo. Inoltre hanno promosso l'utilizzo del crisotilo come alternativa sicura in sostituzione delle fibre anfiboliche di amianto. La preoccupazione del Collegium Ramazzini per questo uso protratto dell'amianto ha costituito la base della "Richiesta di Messa al Bando Internazionale dell'Amianto" nel 1999. Al fine di aggiornare la base di conoscenze per raccomandare questa richiesta di messa al bando, il Collegium Ramazzini rende pubblica una posizione aggiornata sui rischi per la salute dell'esposizione ad amianto (XI Collegium Ramazzini Statement). Eur. J. Oncol., 10 (1), 9-30, 2005

Parole chiave: **amianto, rischi per la salute, messa al bando**

Introduction

The health consequences of the use of asbestos in contemporary industrial society have been amply documented in the world scientific literature. This paper reports the current status of health issues supporting the Collegium Ramazzini Statement.

Asbestosis

Asbestosis is a chronic lung disease due to the inhalation of asbestos fibres, either of the amphibole or serpentine type, and is characterized by diffuse interstitial fibrosis and is frequently associated with pleural fibrosis or pleural calcification. X-ray changes are usually small ir-

Received/Pervenuto 15.9.2004 - Accepted/Accettato 27.10.2004
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regular opacities occurring mainly in the lower and middle lung fields. The pulmonary fibrotic changes develop slowly over the years – often progressively, even without further exposures – and their radiographic detection is a direct correlate of their extent and profusion. In some cases, minor fibrosis with considerable respiratory impairment and disability can be present. Pulmonary hypertension is frequently associated with advanced asbestosis and the resultant *cor pulmonale* (right-sided heart failure) may be a cause of death. In some asbestos-exposed cohorts this has accounted for 12-20% of the deaths[1, 2].

Asbestosis is a progressive disease even in the absence of further exposure[3]. Individuals diagnosed with pulmonary asbestosis are at a higher probability of developing and dying of cancer[4-8]. Nine member clinics, from the Association of Occupational and Environmental Clinics (AOEC)[9], reported seeing 2,057 patients between 1997 and 2000 for asbestos-related conditions, 95% of whom were diagnosed with asbestosis/parenchymal disease principally in occupational categories of the construction industry (Standard Occupational Classification=SOC code 63-64), production working occupations, i.e. welders, labourers, machine operators, etc. (SOC 71, 73-78) and handlers, cleaners and helpers (SOC 86-87).

Most researchers believe that asbestosis is linearly related to cumulative exposure, and because very low concentrations of asbestos do not result in radiological, pathological or clinical evidence of lung fibrosis, this suggests there may be a threshold for asbestosis[10].

Pleural disease

Siegal *et al*[11] reported pleural plaques, in talc workers exposed to talc dusts containing tremolite asbestos. They later noted, after their paper was written, that the experimental production of intrapleural adhesions in animals was reported in the Fifty-Seventh Annual Medical Report of the Trudeau Sanatorium. In the 1950s other observations of pleural calcification and pleural activity were reported in asbestos workers: Smith[12] observed them in tremolite talc workers; Jacob and Bohlig[13] observed pleural thickening among a cohort of 343 cases in Dresden, Germany; Fehre[14] observed pleural calcifications thought to be due to inhalation of silica, however, the author concluded that they were similar to those observed in persons exposed to asbestos dust; and Frost *et al*[15] observed 22 cases of X-ray changes in 31 laggers surveyed from a trade union in Denmark, with 19 having had pleural abnormalities including pleural thickening and calcifications. A review of 6 studies, on the complications of pleural plaques in asbestosis patients in China, found a range of plaques from 34.2% to 100% and in another 6 studies on asbestos workers the prevalence of pleural plaques ranged from 1.3% to 29.8%[16].

Calcifications resulting from fibrous dust are usual bilateral, and situated on the parietal pleura; probably very small amounts of dust are capable of causing pleural calcifications which appear to be due to mechanical irritation[17]. The plaques are progressive and sometimes cause adverse respiratory symptoms, such as dyspnoea (breathlessness) and decrements in pulmonary function while it is more likely that diffuse pleural thickening will cause functional impairment[18-21]. Pleural thickening is considered a marker of past exposures by some authors[22].

There is evidence that people with pleural plaques are more likely to develop asbestos-induced parenchymal fibrosis than those without such plaques[23]. Furthermore, in occupationally exposed persons, appreciable amounts of fibres were found in their thoracic lymph nodes as well as in pleural plaques[24, 25]. In some situations, asbestos-induced pleural plaques were the most common finding of the asbestos-related abnormalities[10]. Asbestos and erionite fibres appear to be the only causative agents for the typical pleural plaques with a usual latency of several decades. Other authors believe that there is evidence that individuals with asbestos-induced pleural plaques are at a markedly increased risk of developing and dying of lung cancer or malignant mesothelioma.

Fletcher[26] reported that asbestos-exposed shipyard workers, diagnosed with pleural plaques, none of whom had radiological evidence of asbestosis, were at a 137% increased risk of dying from lung cancer (16 observed *vs* 6.74 expected; $p<0.005$; calculated relative risk=RR: 2.37, 95% confidence interval=CI: 1.36-3.86), a 290% increased risk of dying from mesothelioma (3 observed *vs* 0.10 expected; $p<0.001$; calculated RR: 30; 95% CI: 6.19-87.67) and a 55% increased risk of other cancers when compared to the general population of the same age, but not occupationally exposed to asbestos. The workers included a variety of crafts workers.

In another study on shipyard workers, Edge[27] reported that workers with mixed asbestos exposures and pleural plaques (without evidence of pulmonary fibrosis) had a 2.5 times increased risk of developing carcinoma of the bronchus, when compared to the matched controls without plaques who had a 1.2 times increased risk: the difference probably reflected the dose. Edge also observed 3 mesotheliomas in subjects with plaques while none occurred in those with no plaques. In a later study of shipyard workers, Edge[28] found in a group of 156 workers with asbestos-induced pleural plaques, but with no other radiographic evidence of pulmonary fibrosis, 8 deaths from lung cancer, compared to 3 in those without pleur-

al plaques (a 2-fold increase) and 13 mesotheliomas among those with plaques compared to 2 in those without plaques (a 6-fold increase). Smoking could not explain the increase in lung cancer in these workers. Edge also observed that, if he removed the one case of mesothelioma that occurred within the first 2 years of observation, the 7 cases that occurred in 2,637 man-years of observation, gave an incidence of 1/377 cases per year.

Hillerdal[29] indicated several factors related to pleural plaques: first, plaques are always more widespread on autopsy than in X-ray; second, in populations without endemic plaques, 80-90% of the strictly defined plaques are due to occupational exposures and they can also be found in persons with low-level exposures; third, asbestos bodies are more prevalent in people with pleural plaques; fourth, pleural plaques are more related to time after exposure to asbestos than to the dose; fifth, in industrially developed countries 2-4% of all males over the age of 40 usually have plaques; sixth, plaques themselves are usually harmless but, as a marker of exposure, they are indicators of sufficient latency for asbestos-induced cancers, i.e. persons with pleural plaques are twice as likely to develop lung cancer as those without such plaques, and those with plaques are at greater risk of mesothelioma; seventh, those with pleural plaques, in general, have lower lung function; and finally, eighth, people having high rates of pleural plaques from living in areas of local deposits of asbestos, such as tremolite, amosite and crocidolite, have a high risk of mesothelioma, while those with high rates of pleural plaques living in areas of anthophyllite do not. In residents of Da-yao (China) with environmental exposure to crocidolite, pleural plaques were prevalent in 11% of those over 20 years of age and in 20% in those over 40 years old[30].

Pleural effusions, diffuse pleural thickening and rounded atelectasis are also caused by exposure to asbestos[31].

Lung cancer

In early studies asbestosis was frequently found in conjunction with lung cancer among workers exposed to asbestos[5, 32, 33]. This lead some scientists to speculate that asbestosis was necessary and somehow associated in the aetiology of lung cancer among those exposed to asbestos, some attributing this association to the "scar" theory of carcinogenesis. This is not strongly supported for all asbestos-associated lung cancers according to Hillerdal[34], since he observed that a majority of tumours were squamous cell cancers and not adenocarcinomas. Adenocarcinomas were found most commonly among patients with asbestosis and in the lower lobes of the lung, where asbestosis is most prevalent[35]. It is true, however, in some cases of advanced asbestosis, that scar carcinomas may develop as an outgrowth of uncontrolled fibrogenesis, just like they do with usual interstitial pneumonitis (UIP), the typical pathologic lesion in asbestosis[36].

Asbestos exposure appears to increase the risk for all histological types of lung cancer[35]. Both those with asbestos exposure and also those with asbestosis have risks of lung cancer higher than those found in the general population not exposed to asbestos[37]. It is more likely that asbestosis is not a precursor of lung cancer, but that both are independent diseases related with a dose-response to exposure to asbestos, and that cancer of the lung can and does occur in the absence of asbestosis[34, 35, 38-40]. McDonald *et al*[41] have presented epidemiological data showing increased risk of lung cancer in occupations with exposure to asbestos in the absence of radiological evidence of pulmonary fibrosis. Hillerdal[34], in a well designed study having sufficient statistical power, found lung cancer to occur in patients with bilateral parietal pleural plaques, but without radiological evidence of asbestosis.

Lung cancer continues to be statistically elevated among asbestos workers under surveillance (standard incidence ratio=SIR: 1.14; 95% CI 1.01-1.26)[42]. In a Chinese study of 8 asbestos factory cohorts and 3 mining cohorts, the complication rate of lung cancer among asbestotics ranged from 3.5% to 26.9%[16]. That exposure levels for carcinogens (including asbestos) are safe is brought into question by the findings that the lungs may accumulate massively more cancer-causing airborne particles than previously thought. The bifurcations within the lung may allow high concentrations of particles to build up as much as 100 times as in the other parts of the lung[43].

Smoking increases the risk of lung cancer not in just an additive way, but in a multiplicative way. Both asbestos and smoking are independently capable of increasing the risk of lung cancer. One of the largest cohorts of asbestos workers to demonstrate this is that of the North American insulators studied by Dr. Selikoff. His co-investigator, E. Cyler Hammond, of the American Cancer Society (ACS), compared a cohort of 12,051 insulation workers, with more than 20 years of work experience, to a control population from the ACS of 73,763 men. The smoking history of both cohorts was known. In this study the RR went up to 53.24 for smoking asbestos insulation workers compared to non-smoking asbestos workers, with 5.17, and non-asbestos insulation workers, as controls, of 10.85[44]. In addition, another summary of smoking and asbestos exposure combined, reported the RR for 3 additional studies to

be 8.2, 32.7, and 25.7[45]. Asbestosis patients had a Standard Mortality Ratio (SMR) of 15.47 (95% CI: 11.2-20.8) for lung cancer[46]. An analysis of 23 studies on asbestos exposure and smoking shows that asbestos multiplies the risk of lung cancer in non-smokers and smokers by a similar factor and that the combined relationship of exposure to asbestos and smoking can be best described by a multiplicative rather than an additive model[47].

The relative risk for lung cancer has varied from 1.0[48] to 17.6[49], with an average RR of 9.8. The prognosis and treatment of asbestos-induced lung cancer is no different than lung cancer having another aetiology. It appears that all cell types of lung cancer occur in asbestos workers and that the presence or absence of one cell type cannot be used to prove or disprove an association of asbestos exposure with the lung cancer[50].

Since 1997 asbestos has been the leading cause of lung cancer in Japan[51].

Most studies of asbestos workers have been conducted among white males, however, when race is considered, black men are also shown to be at a higher risk when exposed to asbestos. One study reports an odds ratio (OR) of 1.8 (95% CI: 1.03-3.1) for lung cancer in black men, however, when using SEER (Surveillance, Epidemiology, and End Results Program) data from 1988-1992 mesothelioma was higher in white men than black (1.7 vs 0.9/100,000)[52].

In a survey of Hungarian workers exposed to asbestos with lung tumours, 72 patients (24%) of 297 had cumulative occupational asbestos exposures assessed as below 25 fibre-years (between 0.01 and 23.9 fibre-years)[53].

In West Germany, a case-control study reported that the results demonstrated a doubling of the lung cancer risk with 25 fibre-years of exposure and, when using a two-phase logistic regression model, showed OR increases from 0 to ≤1 fibre-years (0.86; 95% CI: 0.55-1.33; 1 to ≤10 fibre-years (1.33; 95% CI: 0.80-2.33); and 10+ fibre-years (1.94; 95% CI: 1.10-3.43), which are similar to those found by Stayner *et al* and Dement and Brown[54-56].

A case-referent study of Swedish lung cancer patients found clear evidence for the risk of lung cancer at low-dose levels and showed that the use of linear extrapolation from high exposure levels may underestimate the risks at low doses. For those exposed at 1-2.49 fibre-years the RR was 2.7 (95% CI: 0.7-9.5) in never smokers and for those smoking >20 cigarettes/day, the RR was 80.6 (95% CI: 20.2-322.0)[57]. There is also evidence of an increased number of multiple primary cancers at the same time among those exposed to asbestos compared with the general population[58].

Mesothelioma

Mesothelioma is a cancer of the mesothelium, the thin lining that covers the major internal organs of the body. Its rarity and the fact that this type of tumour is strongly associated with exposure to asbestos make it a "signal tumour". This means that it is considered an epidemiological marker for exposure to asbestos[59, 60].

Wagner was the first to recognize and report primary pleural tumours in 1870[61]. Credit is given to Adami for the term mesothelioma in 1908[62]. The modern concepts concerning the pathology and diagnosis of mesothelioma were set forth in 1931 by Klemperer and Rabin[63]. Gloyne described the migration of fibres to the lymph stream and especially into the mediastinal glands, in a person with asbestosis[64]. It is interesting to note that the lexicographer Hesychius defined asbestosis as stuccoing or plastering and Cooke gave the name asbestosis which now *"may indeed stucco the pleura or the peritoneum"* as well as other organs having mesothelial linings[65]. The dose-response relationship for mesothelioma was first shown among textile workers exposed to asbestos and then among gas mask workers, miners and millers and shipyard workers[66-69].

This uncommon tumour, mesothelioma, is today reported in almost every major study of persons exposed to asbestos. Some have estimated that pleural mesothelioma occurs with an incidence of 1 for every 2 lung cancers; however, these estimates have generally been related to the overall mortality within specific cohorts of asbestos workers and in some cases based on cumulative asbestos exposure of 25 or more fibre-years and can be rather misleading either as overestimates or *vice versa*[53]. In one analysis the authors have thrown out the three highest and the three lowest ratios and then report a range of ratios for mesothelioma to lung cancer from 1.0 to 5.2, however, they actually threw out the 4 lowest so the range is really 0.5 to 5.2 (median 2.4). If they had looked at the entire range it would have a range from 0.3 to 18.5 (median 3.67)[70]. Thus, the actual ratio does vary between studies and any reflection on just the median ratio is misleading. Pleural mesothelioma incidence has been increasing in all asbestos-using countries, despite control measures put in place since the 1970s[71].

Peritoneal mesothelioma is a much rarer tumour than pleural, for example in Sweden the male incidence is 10-fold less than for pleural tumours, but in females it is somewhat higher or about one half that of the pleural tumour. Swedish males have shown no increase in peritoneal mesothelioma since 1985, but in females peritoneal mesothelioma has been steadily increasing and has surpassed the rate of pleural mesothelioma (0.16/100,000)[72]. The US National Institute for Occupational Safety and

Health (NIOSH)[73] in conjunction with the National Center for Health Statistics, reports between 1987-1996 that various work groups had extremely elevated proportional mortality ratios (PMRs) for pleural malignancies. These included insulation workers at 23.08 (95% CI: 10.59-43.80); boilermakes at 15.37 (95% CI: 7.68-27.50); plasterers 11.61 (95% CI: 3.76-27.13); sheetmetal workers 10.35 (95% CI: 6.55-15.54); plumbers, pipefitters and steamfitters 7.02 (95% CI: 5.12-9.40), as well as 13 other specific occupations with PMRs of 2 or greater. They also report these occupations taking place in several industries including ship and boat building and repairing, with a PMR for pleural tumours of 12.60 (95% CI 8.75-17.52) and petroleum refining with a PMR of 5.76 (95% CI 3.29-9.35). Another 15 industries also had PMRs over 2 with all 95% CIs that did not include 1. The finding of such a high PMR for ship and boat building and repair is consistent with the study of Tagnon *et al*[74] of the shipbuilding in coastal Virginia, which found 61 cases of mesothelioma among white males with a RR of 15.7 for the shipyard employees reporting exposure to asbestos, compared to 4.9 for shipyard employees who did not report exposure to asbestos.

The ratio of occurrence of mesothelioma in the pleural area with respect to the peritoneal area appears to be associated with the degree of exposure[75]. Among the large occupationally-exposed groups studied approximately 5-10% of the deaths have been due to mesothelioma[76-78]. In Scotland only 5% of the mesotheliomas had no history of asbestos exposure, while in Canada this lack of association was higher and the Canadian survey gave the annual incidence of about one per million[79]. Other studies have shown the ranges up to as high as 23%[80]. Another estimate has projected that as many as 11% of all asbestos workers' deaths in England will be from mesotheliomas[66]. RRs ranged between 2.3-7.0 with a mean of 4.6 for studies published between 1965 and 1975[81-89]. Mesothelioma association with asbestos exposure has generally been very high, generally over 80%; furthermore those people that did not report exposure, when followed up, have shown such exposures[90]. Dodson *et al*[91] have shown that 10 to 15% of the mesotheliomas arise in the peritoneal area and that fibres also reach the mesentery and omentum in the peritoneal region[92].

In a 1960 report of abdominal cancers, 8 cases of peritoneal cancers were reported in women, 4 of which were suggested to be primary from the ovary and 4 only of the peritoneum and all of the cases were diagnosed with asbestosis. One case was reported in the same series in a male ventilator cleaner with asbestosis[93]. Previously a case of peritoneal cancer had been reported in a 53 year-old asbestos worker with asbestosis, and asbestos fibres were found in the tumour tissue[94]. Three cases of peritoneal mesothelioma were reported among 36 asbestosis cases and another case of peritoneal mesothelioma was reported in an insulation worker[95, 96]. In another series of 72 asbestosis cases, four peritoneal cancers were reported, 1 in a male and 3 in females, 2 of which were thought to be primary ovarian cancers[97]. Eleven cases of peritoneal mesothelioma were reported among 8 men and 3 women between the ages of 38 to 78, with latency periods of 20 to 46 years and exposures between 10 months and 32 years. The authors reported that a "remarkable feature" of the cases was the minimal degree of fibrosis in the lungs[98]. Peritoneal mesotheliomas continued to be reported among various occupations with exposure to asbestos including two cases, one in a 47 year-old and one in a 46 year-old insulator[99, 100], 3 cases among radiologically-confirmed asbestotics[101], 4 among asbestos textile workers[102], 17 cases with known asbestos exposures[103], one case in a 60 year-old former shipyard insulator[104], 3 cases among asbestos textile workers[105], and 4 cases among asbestos textile workers[6]. Newhouse and Thompson[82] reported 27 peritoneal mesotheliomas in London, in some cases, with both occupational as well as domestic exposure.

Mesothelioma continues to remain statistically elevated among asbestos workers, as demonstrated in the Finnish country-wide screening programme of 23,285 men and 930 women between 1990 and 1992 (SIR: 2.77; 95% CI: 1.66-4.31)[42]. Mortality data have generally underestimated the mortality from mesothelioma on death certificates as there has not been a specific International Classification of Diseases (ICD) code to allow adequate coding for mortality analysis, but hopefully the 10th revision of the ICD in 1994 should address this issue: the ICD-10 codes for mesothelioma are C45.0 for pleural and C45.1 for peritoneal. Since it has been generally reported that the incidence of mesothelioma in women is much less associated with asbestos exposure, Steenland *et al*[106] suggest that, if take-home asbestos exposure were considered, the attributable risks may rise to around 90%.

Other sites of mesothelioma have been reported but not with the same incidence as for the pleural or the peritoneal cases, and their relationship to asbestos exposure needs further analysis. Pericardial mesothelioma has also been reported, but it has a very low incidence, as reported in one large autopsy study, of less than 0.0022% and by some estimates is related to about 6% of all mesotheliomas[107]. Dusting of the pericardium with mixed dusts, including asbestos, was reported in an individual when treated for angina pectoris 15 years earlier[108]. Also, congenital malignant peritoneal mesothelioma has been observed albeit very rarely, with only three cases documented and their association with asbestos is unclear[109].

Gastrointestinal tract cancers

The most common other malignant diseases associated with exposure to asbestos are gastrointestinal tract cancers with a RR of 0.5[110] to 3.1[111, 112]. By the 1960s epidemiological studies suggested exposure to asbestos as the cause for the increase in gastrointestinal tract malignancies[113-115].

The Selikoff *et al*[113] study found stomach, colon and rectum cancer increase three times more than expected (29 *vs* 9.4; RR=3.09; 95% CI: 2.07-4.43). Among 370 New York-New Jersey asbestos insulation workers, 12 stomach, colon and rectal cancers were observed when 3.09 were expected (RR=3.90; 95% CI: 2.01-6.81)[112]. During the discussion of the papers, presented at the meeting of the New York Academy of Sciences in 1965, Mancuso reported that he had located 16 additional deaths since his original publication and that 5 of them were cancers[116]. They included one of the stomach, one of the colon, and two of the rectum, which increased his earlier observation of up to 11 gastrointestinal cancers versus 4.55 that would have been expected. Mancuso and El-Attar[111] reported SMRs in the 25-44 year age group of 264 and 1235 after cumulative employment-years of 2.1-7.0 and 7.1-12.0, respectively.

Selikoff[117] found increased rates for cancer of the stomach and oesophagus (20 observed *vs* 6.46 expected, SMR: 3.09; 95% CI: 1.89-4.78) as he did also for cancer of the colon (23 observed *vs* 7.64 expected; SMR 3.01; 95% CI: 1.91-4.52) among the 632 workers, from New Jersey and New York, in his cohort of asbestos insulation workers. In his larger study of 17,800 asbestos insulation workers from the United States and Canada, Selikoff *et al*[118] reported similar observations for cancer of the oesophagus (18 observed *vs* 7.1 expected; SMR: 2.54, 95% CI: 1.50-4.00), stomach (18 observed *vs* 14.2 expected; SMR 1.27, 95% CI: 0.75-2.00), and colon and rectum (58 observed *vs* 38.1 expected; SMR 1.52, 95% CI: 1.16-1.97).

Other authors have observed similar results for gastrointestinal cancers among workers exposed to asbestos in various countries[119-121]. Schneiderman[122], then senior statistician for the National Cancer Institute, in his early version of a meta-analysis of the existing literature, up to 1974, concluded that "increased exposure to inhaled asbestos particles leads to increased digestive system cancer". Newhouse and Berry[123] reported an RR, among male asbestos factory workers with exposure less than 2 years, of 2.11 (20 observed *vs* 9.5 expected; 95% CI: 1.29-3.25 and greater than 2 years of 2.32 (19 observed *vs* 8.2 expected; 95% CI: 1.40-3.62). For females the corresponding SMRs were 2.46 (14 observed *vs* 5.7 expected; 95% CI: 1.34-4.12) and 3.46 (9 observed *vs* 2.6 expected; 95% CI 1.58-6.57), respectively. McDonald *et al*[124] reported abdominal cancers in males with 20 years latency and with cumulative dust exposures of from 10 to 20 mpcf.y of 231.6; from 20 to 40 mpcf.y 247.0; and from 40 to 80 mpcf.y of 383.6, respectively. Nine of the 12 deaths reported were from colon and rectum cancers. Enterline *et al*[125] reported on the mortality of cancer in a cohort of 1074 white males followed to death and found 43 deaths from cancers of the stomach, large intestine, and rectum when 30.99 were expected (SMR: 1.43; 95% CI: 1.03-1.92) with the SMR for stomach cancer being 180.4 ($p<0.05$). A dose-response relationship was reported in a fibre-year analysis for gastrointestinal cancers and years since first exposure: the SMR rate increased from less than one during the first 20 years to 231, 273 and 500 after 20-24, 25-29, and 30-34 years from first exposure[126]. In one of the most recent reviews on the epidemiology of gastric cancer and risk factors, Kelley and Duggan[127] point out that methodological problems have cast doubt on the association of asbestos with gastrointestinal cancers, but that methodological errors had not been discussed; they point to one study that disputes such an association because, after heavy exposure to crocidolite, no excess of gastrointestinal cancers were observed, even though this study itself suffered from a major methodological problem, that being over 25% of the total cohort of 6,506 was lost to follow-up[128]. Albin *et al*[129] reported, among asbestos cement workers, a RR of 3.4 (95% CI: 1.2-9.5) for colon and rectum cancer in those workers with ≥40 f-years/ml. Among pipefitters and boilermakers a case-control study reported an OR for colon cancer of 10.7 (95% CI: 1.07-103)[130].

That it was biologically plausible for the fibre to pass through the human gastrointestinal mucosa, under conditions of the alimentary canal, was shown by Cook and Olson[131], when they were able to show that sediment in human urine contained amphibole fibres. Asbestos fibres as well as asbestos body formation has been shown in tumour tissue taken in the colons of asbestos-exposed workers[132]. Reports of gastrointestinal tract cancers associated with asbestos exposure have been reviewed by the World Health Organization (WHO)[133], in which they have concluded that *"overall, there seems that there is a correlation between lung cancer and gastrointestinal cancer rates in occupational cohorts [exposed to asbestos] which is not due to chance"*. Both the Surgeon General of the United States and the Department of Health, Education and Welfare have concluded that past asbestos exposure can result in an excess of gastrointestinal cancers[134, 135].

Frumkin and Berlin[136] did a meta-analysis of cohort studies to estimate the risk of gastrointestinal cancer mortality. They divided their exposure categories for asbestos exposure into two groups; the first representing heavy as-

bestos exposure, was defined by any cohort having an SMR of 200 or greater for lung cancer and the low exposure category represented by any cohort with an SMR below 200. In the cohort with high exposures to asbestos all of the gastrointestinal cancers, except oesophageal cancer, were significantly elevated with 95% CI that excluded 100. For the low exposure cohorts all of the SMRs were close to 100 for gastrointestinal cancers.

Homa *et al*[137] reported, in their meta-analysis on 20 asbestos-exposed cohorts, that the summarized SMR for colorectal cancer, in those cohorts exposed only to amphibole asbestos, was 1.47 (95% CI: 1.09-2.00) in comparison to those cohorts exposed to chrysotile where it was 1.04 (95% CI: 0.81-1.33).

In a recent study, covering 28 states in the United States, death certificate data was analyzed from 4,943,566 decedents from 1979 through 1990. In the analysis, the authors identified 15,524 cases of gastrointestinal cancer among 12 occupational groups having elevated PMR for mesothelioma, a sentinel tumour for exposure to asbestos, and found slightly elevated PMR for oesophageal (108; 95% CI=107-110), gastric (110; 95% CI=106-113), and colorectal cancers (109; 95% CI=107-110). The authors from NIOSH concluded that their large death certificate study supported an association between asbestos exposure and some gastrointestinal cancers[138]. The results of a mortality study of textile and cement pipe manufacturers, between 1933 and 1980, found statistically significant colon cancers (27 observed *vs* 14.78 expected; SMR 1.83; 95% CI: 1.20-2.66)[139].

Stomach cancer increased among rubber workers engaged in the early production stages of mixing and weighing which, the authors concluded, may point to the rôle of either asbestos-contaminated talc or carbon black, but their results do not support the causal rôle of nitrosamines[140]. The rôle of carbon black in the aetiology of stomach cancer is not supported[141]. A risk of stomach cancer was evaluated for 12 workplace hazards, including asbestos, which did not find any significant relationship. The study was a death certificate analysis from 24 states in the United States using exposure data from a variety of sources including two textbooks, computerized databases from the Occupational Safety and Health Administration (OSHA) and NIOSH, unpublished industrial hygiene reports and personal experiences. The exposure surveys based on the computerized databases, while containing some quantifiable data, are mainly based on subjective interpretation by the surveyors. Any use of the two textbooks for exposure classification is very questionable since the very limited exposure data reported conversion from mpcf.y to fibres/ml and one of the authors warns using such conversions is done "*…with considerable risk to the validity of the results*"[142]. Readers of the paper cannot judge the author's conclusions adequately when these are based on unpublished industrial hygiene data or personal experiences; given these factors of limited validity, the author's conclusions must be questioned[143].

Limited evidence has also been shown for associations between gastric cancer and asbestos exposure.

A digestive cancer registry kept since 1978, in a plant manufacturing fireproof textiles and friction materials was analyzed[144]. The study found significant excess of peritoneal cancer, and more than expected deaths for other digestive cancers: this led the authors to conclude that there was sufficient initial evidence to suggest a relationship between occupational exposure to asbestos and risk of digestive cancer, and that evidence of a dose-effect relationship can be seen among the whole population at risk. An important finding of this study is that the authors feel that intensity of exposure is more important than its duration.

A multicentre case-control study in Italy involved interviews with 640 histologically confirmed male cases and 959 controls, randomly selected from the resident populations of the study areas. Workers with 21 or more years of potential exposure had non-significantly increased risks related to asbestos exposure[145].

A study of 1,756 male workers at a nitrate fertilizer plant, employed for one year or more between 1947 and 1980, using asbestos and nitrogen derivatives as indicators of individual exposure, found a slight increase for stomach cancer (28 observed *vs* 19.9 expected; RR: 1.41; 95% CI: 0.93-2.03)[146].

A study was conducted on Norwegian lighthouse keepers, exposed to asbestos in their drinking water, which came from cisterns, collecting rain water off the roofs, made of asbestos-cement tile. Fibre counts ranged from 1,760 to 71,350 million fibres per litre; these were higher that those measured in the general Norwegian water supplies. Measurements were taken 20 years after the roof tiles were installed and those keepers with 20 years latency or more experienced a stomach cancer incidence of 11 observed when only 4.57 were expected (RR: 2.41; 95% CI: 120-431)[147]. These increases for stomach cancer were occurring during a period of time when the overall rate of stomach cancer was going down, for males and females in all age groups, in Norway[148].

Case reports have also identified associations between exposure to asbestos and gastrointestinal cancer. Case reports taken alone and without connection with the numerous epidemiological studies, as discussed previously, would be mostly of clinical interest or suggestive of hypothesis generation, however, when connected with the well controlled and conducted epidemiological studies, they are of much greater importance.

In a series of five cases of double cancers involving the lung and the stomach and after determining if the subjects had exposure to asbestos, three had such occupational histories and many crocidolite fibres were found in their autopsied lungs. The authors suggested there could be an association between these three cancers and their exposures to asbestos[149].

One case report, of an 84 year-old man with pleural plaques with calcification and a history of shipyard work giving known asbestos exposure, presented with a double cancer of the stomach and colon. Asbestos bodies were also found in his autopsied lung tissue. Given the epidemiological literature the authors suggested that there might be an association with exposure to asbestos[150].

In a series of 35 primary multiple cancers, confirmed by autopsy, 25 (71%) were proven to have had exposure to asbestos. Among these cases, lung and stomach cancers were the main component of the multiple cancers and, in addition, 13 of the cases had more than 1000 asbestos bodies in five grams of autopsied wet lung tissue. The authors, given the epidemiological literature, suggested that asbestos exposure might possibly have induced a high incidence of multiple cancers. Kishimoto and Shimamoto[151] continuing their evaluation of case reports, in this later publication reported on 10 cases of double cancers of the lung and stomach. Five of the cases had developed their cancers simultaneously, while the other 5 had developed their lung cancer after stomach cancer surgery. Eight of the cases had histories of asbestos exposure, and almost all cases had significantly high numbers of asbestos bodies in autopsied lung tissue. The fibre type found in the lungs was all chrysotile.

The final case report by Kishimoto and Yamaguchi[152] described a 76 year-old male with simultaneous double cancer of the lung and stomach. Histologically the two tumours were different (stomach: well differentiated tubular adenocarcinoma; lung: moderately differentiated papillary adenocarcinoma); while the stomach cancer was at an early stage, the lung cancer was at stage IIIa. The case had a definite exposure to asbestos in a Japanese naval shipyard. On X-ray, pleural plaques with calcification were found as were numerous asbestos bodies in resected lung tissue which were chrysotile and tremolite. Even though the patient was a heavy smoker, the authors suggest that asbestos exposure and smoking are considered aetiological factors independently and synergistically for cancer development.

Laryngeal cancers

Doll and Peto[153] have suggested exposure to asbestos as a risk factor for cancer of the larynx. The IARC, of the WHO, reported in 1977 and again in 1987 about an excess of cancers of the larynx observed in workers exposed to asbestos. In a review of 12 cohort studies, half did not show any significant excess in laryngeal cancer and the other studies had SMRs that ranged from 1.91 to 5.41; however, the authors contend that none had adjusted for confounders such as alcohol and smoking[154]. Looking at 6 cohorts with lung cancer RR of 2 or more they found two with the highest RR estimates for lung cancer of 4.06 and 3.28, which gave strong findings for asbestos exposure and laryngeal cancer with RRs of 1.91 (90% CI: 1.00-3.34) and 3.75 (90% CI: 1.01-9.68). Confounders of smoking and alcohol consumption did not explain the excess[155].

Edelman[156], reviewing 13 cohort studies, found two studies out of 13 with SMRs that were statistically increased for laryngeal cancer from asbestos exposure. While no causal association was found among 322 workers examined at a friction products manufacturing plant, 20% with asbestos exposure had laryngitis when compared to only 11% in the lower risk group and the authors concluded that asbestos may act as an irritant to the larynx[157]. Maier and Tisch[158] found that the majority of laryngeal cancers were identified in blue collar workers exposed to a variety of hazards including asbestos, but did not make any conclusions concerning a causal association. A case-control analysis of 112 patients in Uruguay found an OR of 2.4 (95% CI: 1.2-4.8) for those exposed to asbestos for over 21 years[159].

A meta-analysis of 69 asbestos-exposed occupational cohorts found a meta-SMR of 157 (95% CI: 95-245) with latency of at least 10 years and a meta-SMR of 133 (95% CI: 114-155), without any latency association, but when analyzed by work group they found meta-SMRs for latency among asbestos miners and millers (135; 95% CI: 124-146); asbestos products manufacture (192; 95% CI: 176-209); and friction materials workers (112; 95% CI: 101-124). Without latency asbestos miners and millers had a meta-SMR of 153 (95% CI: 144-163, p=0.002) and asbestos products manufacturers of 188 (95% CI: 173-203, p=0.0001). Based on these results the authors concluded there was a suggestion of an association between asbestos and laryngeal carcinoma[160].

Asbestos exposure was related to a RR of 1.8 (95% CI: 1.1-3.0) in the highest exposure group, in a case-control study of 545 cases of squamous cell cancer of the upper gastrointestinal tract compared to 641 referents, among Swedish men aged 40-79, living in two regions between 1988-1990[161].

A French study on asbestos exposures, controlled for both smoking and alcohol, found an excess in hypopharynx cancers (OR: 1.8, 95% CI: 1.1-2.7) which was con-

sistent with an IARC case-control study which found an OR of 2.1 (95% CI: 1.2-3.8) associated with cancers of the hypopharynx and epilarynx, both of which are contiguous with similar clinical characteristics, thus making an aetiology of common cause plausible. The highest risk was for the epilarynx at the highest asbestos exposure (OR 2.22; 95% CI: 1.05-4.70). The authors found a non-statistical excess for laryngeal cancer which they concluded points into the same direction as those significant for the subsites. The authors did not find any significant interaction between smoking and asbestos for laryngeal cancer[162].

In a Japanese study of 525 autopsy cases of asbestosis between 1958-1996 compared to 1,055,734 non-asbestosis cases, laryngeal cancers were significantly higher (6 observed *vs* 3 expected or 1.1% compared to 0.3%, $\chi^2=12.0$, $p<0.001$)[163].

In a study by Browne and Gee[164] of mortality and morbidity prospective studies, the authors found that only one of the mortality studies had clear evidence of an excess for laryngeal cancer (8 observed *vs* 3 exposed; SMR 2.7, 95% CI: 1.15-5.25) and of two morbidity studies one study had a significant excess for those hired between 1928 and 1940 (5 observed *vs* 0.9 exposed; SMR: 5.5; 95% CI: 1.8-12.9) which was not found in those hired after 1940 (9 observed *vs* 7.5 exposed; SMR: 1.2; 95% CI: 0.55-2.28). The later finding might reflect an inadequate latency factor for those hired after 1940. It appears that the authors grouped their analysis together for the 22 mortality studies and then summed the observed and the expected values, for all studies, and then calculated a SMR for the total in order to come to the conclusion that there was no causal association between asbestos and laryngeal cancer, a technique not epidemiologically valid for such analysis without weighing the studies for comparison. In the case-control studies analysis the authors threw out 3 studies because of reported methodological errors and included 17 other studies, on which the authors made no comment as to their methodological accuracy, from which they concluded, based on the non-significance of 15 studies, when compared to the two studies having statistical significance, that no causal relationship exists. Such analysis by equating studies based on only numerical analysis and not considering the various weights of the individual studies is not only misleading, but is in the worst tradition of epidemiology and represents a misapplication of the methods used for meta-analysis.

A NIOSH study of the proportionate mortality among unionized roofers and water-proofers found a statistically significant increase in cancer of the larynx with a PMR of 145 (95% CI: 106-193)[165]. In conclusion, while there is no unequivocal evidence for a causal association between asbestos exposure and laryngeal cancer as compared to asbestosis, lung cancer, mesothelioma and gastrointestinal cancers, the evidence provided by some very well controlled epidemiology analyses does point to such a casual association. That it is biologically plausible is also a factor to consider when evaluating the ability of the asbestos fibre to reach the larynx as is the rôle of inhaled dusts, including those containing asbestos, to cause repeated irritation that may well act as a co-factor in the aetiology of laryngeal cancer[166].

Kidney cancers

Asbestos bodies have been found in the kidney which some scientists feel could either have formed in the lung and then migrated to the kidney, or might have formed around asbestos fibres that had migrated in the kidney; the latter is the theory favoured by Auerbach *et al*[167]. Increased risks of kidney cancer were reported among males in asbestos mining areas of Quebec[168].

Selikoff *et al*[169] reported a RR of 2.3 for renal cancer among 17,800 asbestos insulators under study. In a discussion paper, Cook[170] reported finding fibres in the urine of persons whose drinking water contained amphibole asbestos fibres which were in the same size range, leading him to the conclusion that the kidney is also a target organ for such fibres.

A study of 1,500 asbestos-exposed workers found malignancies of the kidney that the authors considered related to asbestos exposure[171].

A case-control study of renal adenocarcinoma in 518 cases from 37 Massachusetts area hospitals, identified between 1981 and 1984, found the incidence of asbestos-induced renal adenocarcinoma to be 1.6 with a one-sided 95% CI of 1.0 leading the authors to conclude that asbestos was a cause of renal adenocarcinoma[172].

An analysis of three cohorts, having a RR in excess of 2 for lung cancer, identified that all 3 cohorts had excess kidney cancers. Kidney cancers in all three had SMRs of 2.22 (95% CI: 1.44-3.30)[169]; 2.76 (95% CI: 1.29-5.18)[125]; and 1.63 (95% CI: 1.31-2.00)[173]. The authors concluded that the results of their analysis provided good evidence that asbestos can reach the target site for the kidney cancers and, because animal evidence also supports a causal association with kidney cancer, it is probable that asbestos exposure can also cause human kidney cancer[174].

A more recent interpretation of the Smith *et al* study by Pesch *et al*[175] concluded that the Smith *et al* analysis disputed the rôle of asbestos in the aetiology of kidney cancer, whereas this was quite the opposite of the conclusions of Smith *et al*. In a letter to the editor commenting

on the Smith *et al* analysis, Enterline and Henderson[176] concluded that they felt the available data pointed to asbestos as a cause of human kidney cancer.

In a continuing evaluation, through 1986, of the large North American study on insulators, Seidman and Selikoff[177] reaffirmed that the original findings for the major causes of mortality continued, with about the same distributions, including those for kidney cancers.

In New South Wales asbestos was found to significantly increase the risk of kidney cancer (RR: 1.62, 95% CI: 1.04-2.53[178].

McDonald *et al*[179] found elevated kidney cancer incidence in workers having accumulated exposures of 300 mpcf.y, but with no-dose response tendency.

In looking at risk factors for renal cancer in Denmark, a high number of cases were found to be related to asbestos exposure[180].

An international renal-cell cancer study found, when looking at occupation, that asbestos exposure resulted in an RR of 1.4[181].

A review of the case-control studies of asbestos exposure and renal cancers was negative, however, the authors concluded that the power of the studies was too limited, because of the low number of workers exposed, but did report two case-control studies with elevated risks from Denmark and Australia[182]. Kidney cancers were shown to increase after 3 years employment as deck officers among merchant seamen potentially exposed to asbestos (OR 2.15; 95% CI: 1.14-4.08)[183].

Fibre types of commercial usage

Amphiboles

Anthophyllite is a member of the amphibole group with a chemical composition of $(Mg, Fe^{+2})_7Si_8O_{22}(OH,F)_2$. It was principally produced in Finland up to 1974, where it was widely used[184, 185]. Mesothelioma from exposure to anthophyllite was not recognized until much later than that due to the three major commercial fibre types (amosite, chrysotile and crocidolite). It is now clear that mesotheliomas occur among anthophyllite asbestos-exposed workers[10, 186-188]. In one study 4 mesotheliomas were observed when the authors expected 0.1 (SIR=40; 95% CI: 10.90-102.42, as calculated by Lemen)[110].

Amosite is a member of the amphibole group with a chemical composition of $(Mg,Fe^{+2})_7Si_8O_{22}(OH)_2$ (cummingtonite-grunerite). It was mainly used in asbestos-cement sheets, thermal insulation and roofing products and commonly referred to as brown asbestos[184, 185, 189].

Crocidolite is a riebeckite mineral of the amphibole group, with a chemical formula of $Na_2Fe_3^{+2}Fe_2^{+3}Si_8O_{22}(OH,F)_2$. It is often referred to as blue asbestos and is more brittle, with harsher texture, which explains why it is not used in a lot of commercial products such as friction products due to its ability to score the drums of the brake[185, 189, 190].

Tremolite is a tremolite-actinolite mineral and is found in the amphibole group, even though it is often referred to only as tremolite; it has a chemical formula of $Ca_2(Mg, Fe^{+2})_5Si_8O_{22}(OH,F)_2$. Tremolite is often found as a contaminant of chrysotile asbestos or talc[185, 189-191]. It has been suggested that milling will remove the tremolite from chrysotile, however, this is not universally accepted[192].

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Tremolite, mesothelioma and lung cancer

Persons using a pure form of tremolite, to mix a whitewash in New Caledonia called "po", have shown a risk of pleural mesothelioma which is strongly associated with its use[193]. Other studies have shown similar associations with tremolite containing whitewashes in Cyprus, Greece, Turkey, and in Corsica where environmental exposures to tremolite deposits occur[194-197]. Associations with lung cancer have been much fewer and seem to be complicated with potential confounding factors such as alcohol, diet, occupational exposures and smoking. Yazicioglu[198] report excesses of lung cancer in areas where the tremolite containing "po" is used.

Serpentines

Chrysotile is the asbestiform variety most commonly used commercially, accounting for some 95%+ of the asbestos ever used and is found in the serpentine mineral group with a chemical formula of $Mg_6Si_4O_{10}(OH)_8$. The non-fibrous forms of this serpentine mineral are lizardite and antigorite. As compared to the amphiboles, the chrysotile fibres are generally finer with high flexibility and good heat resistance and are commonly referred to as white asbestos[184, 185, 189]. The issue of chrysotile-tremolite contamination has been a matter of debate. Some deposits of chrysotile may contain trace amounts of tremolite. Canadian chrysotile is said to be contaminated with fibrous tremolite[191], with less than 1%[199], and with none at all[200]. The world's largest deposits of chrysotile asbestos are found in Russia at the Bazhenovsk deposit in the town of Asbest, close to Ekaterinburg City and accounts for 20% of the world production[201]. This mining area has been mined since 1889 and samples taken and analyzed by phase contrast microscope (PCM) and scanning electron microscopy (SEM) found only chrysotile and no am-

phibole minerals; however lung tissue analysis did find tremolite[202].

In an analysis of lung tissue of 6 Chinese chrysotile miners, all of the bulk samples contained amphibole asbestos (measuring about 0.002 to 0.310% lung tissue) with tremolite fibres found in every sample. While few studies have examined impurities of Chinese chrysotile, with the exception of qualitative analyses of the Qilian mine which showed "little amount" of amphibole and the Chaoyang mine, Liaoning province, which also found a small amount of tremolite[201]. Zimbabwe is also a major producer of chrysotile asbestos and tremolite was not found in samples taken for an epidemiology study[203, 204]. In samples taken from another major deposit of chrysotile, in a mine and mill in Balangero, Italy, no tremolite was detected in any of the samples of chrysotile[205].

The carcinogenicity of chrysotile asbestos

Simson[206] reported fibrosis and golden yellow bodies in the lungs of guinea-pigs similar to those found in humans. The animals were exposed 2 hours per day for 50 days to chrysotile.

Results from animal bioassays present a strong case that there is no safe form of asbestos. Wagner *et al*[207], then with the UK Medical Research Council (MRC), have shown that a commercial grade Canadian chrysotile, which is used primarily for paint and plastic tile fillers, can induce mesotheliomas when injected intrapleurally into rats, and induce primary lung neoplasms when the animals are exposed by inhalation. Not only does it appear that chrysotile is as potent as crocidolite and the other amphiboles in inducing mesotheliomas after intrapleural injections[208], but it is also equally potent in inducing pulmonary neoplasms after inhalation exposure[209]. In terms of degree of response related to the quality of dust deposited and retained in the lungs of rats, chrysotile appears to be much more fibrogenic and carcinogenic than the amphiboles[209].

Epidemiologic evidence combined with animal data supports the hypothesis that all fibre types, including chrysotile, are responsible in the aetiology of lung cancer and mesothelioma as well as other cancers. While most of these studies are of cohorts of workers who were exposed to chrysotile that may have been contaminated with low levels of tremolite, several studies revealed a substantially increased risk of contracting mesothelioma from exposure to chrysotile that did not contain any tremolite contamination. In the first study, Piolatto *et al*[205] examined a cohort of 1,094 chrysotile production workers employed at the mine and mill in Balangero, Italy, a site where no tremolite was detected in any of the samples of chrysotile. Among the 427 deaths, the authors discovered two mesothelioma cases, one confirmed pathologically and one based on radiographic findings and an examination of pleural fluid. While the authors did not report a SMR, in this cohort, it could however be expected that the SMR would have been greater than 2 given the rate of one mesothelioma in 10,000 deaths.

In a similar study, Cullen and Baloyi[203, 204] examined the records of Zimbabwean miners and millers who had been certified as having an occupational lung disease. Like the chrysotile ore mined in Balangero, Italy, no tremolite was detected in any of the samples. The authors estimated that 6,647 Zimbabweans were engaged in the mining and milling operations at two mines: Shabani and Goths. Among the chosen cohort of 27 miners with sufficient documentation, the authors discovered one mesothelioma case proven by biopsy, one mesothelioma proven by post mortem and one probable mesothelioma based on radiographic findings. They also reported one case of asbestosis, with probable terminal mesothelioma or lung cancer, based on chest X-ray only as having a pleural mass 5 years later. Given the rarity of the disease and the size of the exposed population, and even though the authors did not report an SMR it is most likely that it would have exceeded an SMR of 2, given the rarity of the disease in a comparison population of non-exposed individuals.

Rogers *et al* examined 221 cases of definite and probably mesothelioma obtained from the Australian Mesothelioma Surveillance Program[210, 211]. Among these cases, Rogers recorded a substantial number of mesothelioma patients in whom the only detectable type of asbestos was chrysotile, with evidence of a dose-response effect, as reflected in a trend to an increasing OR at relatively low fibre concentrations of less than 10^6 fibres per gram dry lung tissue ($\log_{10}$: 5.5-6; OR: 8.67).

A 25-year longitudinal study of workers exposed to amphibole-free chrysotile found two confirmed cases of mesothelioma among the exposed workers[212]. The RR for all cancers, adjusted for smoking and age, was 4.29 (95% CI: 2.17-8.46).

In addition to the studies of uncontaminated, "pure" chrysotile, there have been several studies of populations who were exposed to chrysotile ore and processed chrysotile products, which contained trace amounts of the amphibole tremolite. In the mining context, Camus, Siemiatycki and Meek[213] compared mortality among women in two chrysotile asbestos mining areas in the province of Quebec with mortality among women in 60 control areas. While focussing on lung cancer mortality, the authors discovered a statistically significant increase in mesotheliomas, as evidenced by an SMR of 7.63 (95% CI: 3.06-15.73).

With regard to processed products composed of principally chrysotile asbestos, Nokso-Koivisto and Pukkala[214] examined a cohort of 8,391 members of the Finnish Locomotive Drivers' Association during the years 1953-1991. They found a statistically significant four-fold increased risk of mesothelioma. In another study of railroad workers predominantly exposed to chrysotile asbestos, Thomas Mancuso arrived at a similar conclusion[215]. Out of a cohort of 181, there were 156 deaths, 14 of which were identified as mesotheliomas, constituting 34% of all cancer deaths in the study, the incidence of mesothelioma far exceeding a doubling of the risk.

Also published is a study on workers employed in an asbestos textile, friction and packing manufacturing facility, which utilized 99% chrysotile asbestos. Among the deaths observed in this study, 17 were the result of mesotheliomas, representing 4.3% of the deaths. It was concluded that the study demonstrated an excess risk of mesothelioma in both the males and females[216].

Dement and Brown[55], in a cohort of chrysotile textile workers, found an overall excess of respiratory cancer with an SMR of 2.25 (95% CI: 1.85-2.71) and an SMR of 2.24 (95% CI: 1.83-2.72) for pleural mesothelioma. The chrysotile fibres came exclusively from Quebec, British Columbia, and Zimbabwe. In the manufacturing process the fibres mixed with cotton were sprayed with a light mineral oil, which saturated it to about 4% and by the time it reached the spinning looms the oil had diminished to less than 1%. Some have purported that this study's findings might be a result of the mineral oil treatment, however, the authors found from a case-control analysis that only a slight exposure-response reduction occurred for lung cancer when the mineral oil exposures were adjusted for, thus leading the authors to conclude that the mineral oil exposures were insignificant.

Finally, Sturm *et al*[217] reviewed 843 cases of mesothelioma recorded in the German Federal State of Saxony-Anhalt between 1960 and 1990. Sixty-seven cases, representing 14% of the total, were directly attributable to a sole exposure to chrysotile asbestos.

When comparing animal studies to human response, based on the epidemiology studies, Kuempel *et al*[218] of NIOSH, concluded that chrysotile toxic doses (TDs) in rats compared to humans. Their analysis found that the rat-based risk estimates for lung cancer compared to humans were reasonably concordant to those for the Canadian miners/millers studies while those compared to textile workers were much higher, indicating that humans may be more sensitive. However, fibre size studies were not conducted, but there is evidence that textile workers may have been exposed to longer fibres than those found in the Canadian cohorts.

The 1984 Report of the Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario concluded that "*all fibre types can cause all asbestos-related diseases, …*"[219]. This supported the finding of reported cases of mesothelioma among brake mechanics exposed to chrysotile[220, 221]. Mancuso[215,222] further contended, based upon his analysis of railroad machinists, that commercial chrysotile asbestos has caused mesotheliomas and that the risk is greater than previously asserted. There is further concern that chrysotile is rarely found in its pure form and that most chrysotile deposits are contaminated with the amphibole tremolite, which is agreed by experts to be a toxic form of asbestos[223]. In a review of the evidence, Stayner, Dankovic and Lemen[224], of the NIOSH, concluded that "*given the evidence of a significant lung cancer risk, the lack of conclusive evidence for the amphibole hypothesis, and the fact that workers are generally exposed to a mixture of fibers, we conclude that it is prudent to treat chrysotile with virtually the same level of concern as the amphibole forms of asbestos*". Further discussions on the causal connection between chrysotile asbestos and mesothelioma can be found in Lemen[225].

Two publications highlight the fact that the majority of the world medical community considers chrysotile to be a cause of peritoneal mesothelioma. In 1997, a multidisciplinary gathering of nineteen pathologists, radiologists, occupational and pulmonary physicians, epidemiologists, toxicologists, industrial hygienists, and clinical and laboratory scientists held a meeting in Helsinki, Finland to agree upon criteria for attribution of disorders of the lung and pleura in association with asbestos. Collectively, the group had published over 1,000 articles on asbestos and asbestos-associated disorders. The consensus of the group was that *all types* of malignant mesothelioma can be induced by asbestos, with the amphiboles showing greater carcinogenic potency than chrysotile[31].

The second publication was a monograph devoted specifically to chrysotile asbestos, that was prepared by the International Programme on Chemical Safety (IPCS) in conjunction with the WHO. After an extensive review of the world literature, this body concluded that *"commercial grades of chrysotile have been associated with an increased risk of pneumoconiosis, lung cancer and mesothelioma in numerous epidemiological studies of exposed workers"*[226].

Chrysotile fibres are much more chemically and biologically reactive than amphibole fibres and, because of this reactivity with the tissues, they lose their structural elements and divide into smaller fibrils, making their recognition difficult by the usual analytical methods. In fact, many of the fibres are removed from the lung and

exhaled back through the bronchi or removed by the lymphatic system to other organs of the body[227-230]. The concentration of dust in the lungs of rats exposed to Canadian chrysotile was only 1.8-2.2% of the dust concentration in the lungs of animals exposed to amphiboles (after 24 months of inhalation exposures). Yet the lung tumour incidence and degrees of pulmonary fibrosis were similar in all groups. These findings support the idea that chrysotile fibres cause more cellular injury, fibrosis and lung cancer than the amphiboles, while at the same time are less readily detected in the tissue after the damage is done. Churg *et al*[231] concluded that the failure of chrysotile to accumulate in the lung is a result of preferential chrysotile clearance during the first few days to weeks after exposure and that dissolution plays no rôle in the clearance and that the preferential clearance may be a result of fragmentation and rapid removal of the chrysotile fibres. This is also supported by Roggli *et al*[192], in that they conclude, as do others, that chrysotile does not accumulate in lung tissue because its fibres are broken down into smaller fibrils that are rapidly cleared from the lung. Such chrysotile fibres have been missed by their technique which counted only fibres longer than 5 μm in length. They also conclude that long, thin fibres would likewise be missed, because chrysotile content is poorly detected by the SEM, and thus fibre burden is a poor indicator of total chrysotile exposure and other information must be sought in order to address the question of total body burden of chrysotile. Suzuki *et al*[232], in 92 consecutive cases of mesothelioma, observed that the major asbestos type identified in the mesothelial tissues was chrysotile when compared to the chrysotile fibre burden in the lungs of the same cases (79.0% *vs* 28.3% respectively). It was found that dogs with mesothelioma had higher concentrations of chrysotile in their lungs than the control dogs[233].

Malorni *et al*[234] suggested that fibre penetration could rearrange the cytoskeletal apparatus of the cell and that this could indicate an interaction between the chrysotile fibres and the normal mitotic process, since giant multinucleated cells are formed. Churg *et al*[235] further believe that the short fibres may be more fibrogenic than previous animal data suggest and deserve further study.

Biologic plausibility seeks to determine if the theory of causation fits known mechanisms of injury causation. While it is impossible to have a complete understanding of the mechanisms of cancer causation, the biologic facts known about the various asbestos fibres and how they cause disease are consistent with the postulate that chrysotile asbestos fibres are capable of producing mesotheliomas.

First, it has been long known that it is not the chemical composition of the various asbestos fibres that is important in their ability to produce disease: the health effects of asbestos are related primarily to their morphology, shape and size. Many researchers contend that the potency of crocidolite is related to its thin diameter. Similarly, chrysotile fibres have a tendency to cleave longitudinally creating extremely thin fibrils.

Second, it is universally accepted that chrysotile asbestos is carcinogenic and capable of causing or contributing to the development of lung cancer.

Third, mesotheliomas develop in the pleura, peritoneum and other serosal surfaces of the body. It is universally accepted that chrysotile is a cause of cancer in the lung and that it also migrates to the mesothelial linings of the body[232, 236-238]. Sebastien *et al*[239] found that all the fibres in the pleura were chrysotile when there was no predominance in the parenchymal samples, leading the authors to conclude that lung parenchymal retention is not a good indicator of total body burden of asbestos retention. Translocation of asbestos fibres to other organs is also well documented. In addition, a series of 168 cases of mesothelioma reviewed by Suzuki and Yuen[236] confirmed:

"1. Asbestos fibers were present in almost all of the lung and mesothelial tissues from the mesothelioma cases. 2. The most common types of asbestos fibers in lung were either an admixture of chrysotile with amphiboles, amphibole alone, and occasionally chrysotile alone. In mesothelial tissues, most asbestos fibers were chrysotile. 3. In lung, amosite fibers were greatest in number followed by chrysotile, crocidolite, tremolite/actinolite, and anthophyllite. In mesothelial tissues, chrysotile fibers were 30.3 times more common than amphiboles. 4. In some mesothelioma cases, the only asbestos fibers detected in either lung or mesothelial tissue were chrysotile fibers. 5. The average number of asbestos fibers in both lung and mesothelial tissues was two orders of magnitude greater than the number found in the general population. 6. The majority of asbestos fibers in lung and mesothelial tissues were shorter than 5 μm in length".

Since chrysotile is carcinogenic and is present in high concentrations in the mesothelial linings where the mesothelioma is induced, it is biologically plausible that it causes or contributes to the cause of mesothelioma. This is also shown by many mechanistic and molecular studies that indicate how chrysotile may cause mesothelioma. Fibre penetration can rearrange the cytoskeletal apparatus of the cell and this could indicate an interaction between the chrysotile fibres and the normal mitotic process, since giant multinucleated cells are formed. These studies indicate that chrysotile penetrates the cell, enters the nucleus and induces abnormal chromosome formations in divid-

ing cells[234]. Some of these abnormalities include the deletion of the p53 gene growth[240]. Inhaled chrysotile asbestos induced, at the fibre deposition sites, the expression of p53 protein[241], which suggests that the p53 protein can accumulate in the lung tissue after chrysotile exposure.

Additionally in a study of the phosphorylation of the p53 protein in A549 human pulmonary epithelial cells, exposed to asbestos, it was found that chrysotile asbestos, on a per-weight basis, was more potent in inducing Ser15 phosphorylation and accumulation of the p53 protein than crocidolite[242].

Another recent study has indicated that particle stimulation chemiluminescence (CL) production by polymorphonuclear leucocytes has been used to evaluate the pathogenicity of mineral fibres in the understanding that reactive oxygen metabolites as measured by CL are aetiopathogenically related to fibre toxicity. These findings may indicate that neither the total number nor the specific range of fibre dimensions are solely determinate of the CL production and thus other physiochemical factors, like surface reactive characteristics of the milled fibres may play a rôle in the aetiology of disease[243].

Pott[244] has questioned fibre dimension as a reliable yardstick for the carcinogenic dose and has pointed out that inhalation studies of rats, as a surrogate for human inhalation effects, are misleading in that rats are known obligatory nose breathers. These findings bring into question the Stanton *et al* hypothesis[245] on fibre diameter and length being the only determinates of the carcinogenicity of fibres. Pott[244] also addresses the use of intrapleural and intraperitoneal routes in examining the carcinogenic potential of inorganic fibres, which has been criticized emphatically. Pott concludes that the consistency of such an argument is not supported when, for example, the inhalation studies with crocidolite do not result in either lung tumours or mesothelioma, even though the fibre concentrations in the lung are very high.

The epidemiological findings along with the results of the experimental studies leave no doubt that the scientific evidence supports the carcinogenicity of chrysotile alone in the induction of mesothelioma.

Are exposure standards effective?

The current standards for the "supposedly" safe use of asbestos have all been shown to be not effective. Except for bans, the lowest occupational exposure standards do not prove adequate protection from exposure to asbestos. This has been demonstrated through adequately performed risk-assessments, which have been criticized as risk-assessments based on exposures from epidemiology studies of workers exposed at much higher concentrations; however, the Collegium Ramazzini believes such risk assessments do adequately predict future disease potential and cannot be discounted.

The United States standard for asbestos is currently 0.1 fibres/cc over an 8 hour time-weighted average, which equates to the inhalation of 1,200,000 fibres per day. The exposure-response relationship for lung cancer is linear[246]. At this current standard the risk of death is 3.4 per 1,000 at 0.1 fibres/cc[3]. Even at this new limit it can be clearly seen that the risk of dying from cancer is not zero nor does it even approach it. Dement and Brown[55] reported a statistically significant excess of lung cancer at exposures as low as less than 3 fibres/year. Case reports exist, also some epidemiological evidence, of short exposures in the order of a few days to months that give rise to asbestos-related cancers[247].

The WHO[133] stated that *"[T]he human evidence has not demonstrated that there is a threshold exposure level for lung cancer or mesothelioma, below which exposure to asbestos dust would not be free of hazard to health"*. The IPCS has reiterated this position[226]. These conclusions continue to support what the industry said in 1965, that the only safe level to prevent disease is zero, and it also supports the finding that non-malignant respiratory diseases need not be present before cancer of the lung or mesothelioma can develop.

There is marked enhancement of the risk of lung cancer in workers exposed to asbestos who also smoke cigarettes[44, 76, 248, 249]. Data from Hammond *et al*[44] and Weiss[250] suggest cigarette smoking may also contribute to the risk of asbestosis. Smoking, however, has not been found to be associated with an increased risk of pleural or peritoneal mesothelioma, or cancers of the stomach, colon and rectum, which occur with equal frequency among smoking and non-smoking asbestos workers. OSHA[3] attributes asbestos exposure with 79.4% of the lung cancer deaths among asbestos-exposed workers who smoke and 77.2% of lung cancer deaths among non-smokers.

Toxicity of short asbestos fibres

Any assumption that short fibers, less than 5 μm in length, are not hazardous cannot be justified based on the available science. Because the analytical method of choice, for regulatory purposes, has been the PCM which counts only fibres greater than 5 μm in length, epidemiology studies have been forced to compare doses, in their cohorts, to fibres greater than 5 μm in length. It must be noted that the PCM analytical method was chosen based on its ability to count fibres only and not on a health ef-

fect basis. While PCM has been the international regulatory method for analysis, it is not able to detect small diameter fibres (<0.2 μm in diameter) and because of this, it is suggested that transmission electron microscopy (TEM) should be an adjunct to PCM, since the evidence suggests that PCM may underestimate exposures and the health risks as found in the analysis of brake residue[251].

The assumption that shorter fibres do not cause disease cannot be based on the majority of epidemiological studies to date. Stanton and Wrench[252] and Stanton *et al* [253] found that the longer, thinner fibres were more carcinogenic, but could not identify a precise fibre length that did not demonstrate biological activity.

It must be kept in mind that Stanton has never said that long fibres are bad and short fibres are good; in fact he appreciated that a large number of short fibres, individually of low tumorigenic probability might be more hazardous than fewer long fibres, individually of high probability[254]. It has been shown that it is not the size and shape of the various asbestos fibres that are important in the fibres' ability to produce disease, but other factors may play a rôle in the carcinogenicity of the mineral[255, 256].

Studies have also found that the majority of asbestos fibres in lung and mesothelial tissues were shorter than 5 μm in length, thus indicating the ability of the shorter fibres to reach the tumour site and remain there; therefore their rôle in the aetiology of disease is implicated[236, 257]. NIOSH research has found that, in typical occupational environments, fibres shorter than 5 μm in length outnumber the longer fibres by a factor of 10 or more[258]. Shorter fibres must be studied in more depth and short fibres should not be disregarded especially when clearance is retarded[259]. That chrysotile fibres tend to spit longitudinally as well as partially dissolve, resulting in shorter fibres within the lung, was reported in a review of several articles[55]. Additionally, Fubini[260] argues that, because all forms of asbestos appear nearly equally potent, length and fibre form do not appear influential on the outcome of disease. Fubini makes this conclusion based on work of Boffetta[261] which concludes that the specific type of asbestos is not correlated with lung cancer risk, but that industry specific exposure appears to fit the linear slope best, a finding also supported by Dement and Brown. For mesothelioma, induction was related to the time since first exposure and potency with both industry type and asbestos type[261].

The Agency for Toxic Substances and Disease Registry (ATSDR), in response to concerns about short asbestos fibres resulting from the collapse of the World Trade Towers, asked a contractor to convene a panel of seven experts to evaluate the rôle of short fibres with human disease potential[262]. As to non-carcinogenic lung diseases associated with short asbestos fibres the report concluded that "*…short fibers may be pathogenic for pulmonary fibrosis, and further research is needed to clarify this issue*". The panel concluded that, for carcinogenic effects of short fibres, the current weight of the evidence is that short fibres less than 5 μm "*…are unlikely to cause cancer in humans*". While these conclusions were found in the executive summary of the report, a more in-depth review of the body of the report points to a less conclusive assessment for the rôle of short fibres in the aetiology of cancer. In fact, in panel discussions it was noted that no epidemiologic studies have examined populations exposed only to short asbestos fibres. One epidemiology study that may have the ability to address this issue suffered from short latency to evaluate the development of cancer[263]. Another study of workers having exposure for at least 5 years, in a gold mine with 94% of the asbestos fibres being less than 5 μm in length, found an increased mortality from respiratory cancers (10 observed *vs* 2.7 expected, SMR: 3.7; 95% CI: 1.78-6.81) and non-malignant respiratory diseases (8 observed *vs* 3.2 expected; SMR: 2.5; 95% CI=1.08- 4.93)[264]. A subsequent study[265], looking at the same mine reported above, of miners with 21 or more years underground experience, did not find such an increase for respiratory cancers but did for non-malignant respiratory disease; however, when analyzing the data from the previous study for only those with 20 years or greater years of employment, both respiratory cancers (7 observed *vs* 2.18 expected: SMR: 3.2; 95% CI: 1.29-6.62) and non-malignant respiratory diseases (8 observed *vs* 2.56; SMR: 3.1; 95% CI: 1.35-6.16) were found to be still significantly increased. Two other studies of miners, where 38% of the asbestos fibres were shorter than 5 μm in length, also found excess mortality from lung cancer, mesothelioma, as well as non-malignant respiratory disease, and pointed out that the mortality patterns for mesothelioma were significant because they were much greater than that of crocidolite miners in South Africa and Australia[266, 267].

Animal studies can be misleading when looking at short fibres, especially as rodents clear short fibres from their lungs at a rate approximately 10 times faster than do humans[262]. Experimental models are limited also, due to the fact that only fibres of very limited length distributions have been tested[268]. Further, when appropriate analytical techniques have been used, the overwhelming majority of the asbestos fibres in the tissues have been found to be less than 5 μm in length[268]. Only two of the seven ATSDR panelists felt there was a reasonable certainty of no harm from short fibres, while the other four remained concerned about the ability of short fibres to cause harm[262]. In fact, tremolite asbestos fibres were found to produce the highest average fibrosis grades when exposures were to average tremolite fibres less than 5 μm in length[269].

Conclusions

The grave health hazards of asbestos are well documented in the international literature. The continued use of asbestos in either industrially developed or newly industrial nations is unacceptable.

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Eur. J. Oncol., vol. 10, n. 1, pp. 31-35, 2005

Inquinamento atmosferico delle aree urbane e rischio di cancro

Atmospheric pollution of urban areas and cancer risk

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Riassunto

L'inquinamento atmosferico rappresenta, soprattutto nei paesi industrializzati, uno dei maggiori problemi di sanità pubblica. È stato stimato che in Europa esso costituisca il principale fattore di rischio ambientale e l'ottava causa di morte. È stato riportato che l'inquinamento da polveri fini nell'ambiente urbano determina circa 100.000 morti all'anno ed in particolare che la mortalità per cancro del polmone aumenta di circa l'8% per ogni incremento di 10 μg/m³ di $PM_{2.5}$. Nel presente lavoro si è voluto richiamare l'attenzione su dati da tempo noti ed altri più recenti riguardanti i possibili rischi per la salute (in particolare cancerogeni) derivanti dall'esposizione ad inquinanti atmosferici, ed inoltre prospettare provvedimenti relativi a possibili strategie di intervento. Eur. J. Oncol., 10 (1), 31-35, 2005

Parole chiave: **inquinamento atmosferico, cancro, combustibili, benzina, ottimizzatori di ottani**

Summary

Atmospheric pollution represents, above all in industrialized countries, one of the most important public health problems. It has been estimated that atmospheric pollution constitutes the main environmental risk factor and the eighth cause of death in Europe. It has been reported that fine particulate matter in the urban environment causes about 100,000 deaths per year and, in particular, that each 10 μg/m³ elevation in $PM_{2.5}$ is related with approximately an 8% increased risk of lung cancer mortality. The present publication is aimed at drawing people's attention to data which has long been available and to other more recently known data regarding possible health risks (in particular carcinogenic) caused by the exposure to atmospheric pollutants, and, moreover, to propose measures for possible interventive strategies. Eur. J. Oncol., 10 (1), 31-35, 2005

Key words: **atmospheric pollution, cancer, fuels, gasoline, octane enhancers**

Introduzione

Nei paesi industrializzati, checché se ne dica, l'inquinamento atmosferico rappresenta uno dei maggiori problemi di sanità pubblica. Secondo una recente stima dell'Organizzazione Mondiale della Sanità (OMS), in Europa l'inquinamento atmosferico rappresenta il principale fattore di rischio ambientale e l'ottava causa di morte[1]. Sempre secondo i dati dell'OMS, in Europa l'inquinamento da polveri fini nell'ambiente urbano è responsabile ogni anno di circa 100.000 morti (equivalenti a 725.000 anni di vita perduti)[1,2].

Le sorgenti

Le principali sorgenti di inquinamento atmosferico sono rappresentate da: autoveicoli, industrie (chimiche e raffinerie), impianti di riscaldamento, inceneritori o ter-

Received/Pervenuto 15.10.2004 - Accepted/Accettato 30.11.2004
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movalorizzatori, discariche, incendi, concimi e fertilizzanti utilizzati in agricoltura, etc.

Dagli autoveicoli circolanti deriva circa il 50% delle emissioni inquinanti atmosferiche. Agli inizi del 2000 il parco macchine mondiale constava di 750 milioni di autoveicoli, di cui circa i due terzi concentrati negli USA, nella Comunità Europea ed in Giappone. Attualmente l'Italia, con una popolazione che rappresenta poco meno dell'1% di quella mondiale, ed una superficie che è lo 0,22% delle terre emerse del pianeta, ha un parco macchine di oltre 33 milioni, pari al 4,4% di quello mondiale, ed è al 4° posto, dopo gli USA, la Germania ed il Giappone, per numero di autoveicoli circolanti.

Il consumo annuo di benzina nel mondo è stato valutato in oltre 600.000.000 di tonnellate, di cui circa 300.000.000 negli USA, 130.000.000 nella Comunità Europea, ed oltre 17.000.000 in Italia.

Le emissioni

Gli inquinanti atmosferici sono molteplici. Una recente indagine dell'Environmental Protection Agency (EPA) americana ha evidenziato la presenza nell'atmosfera di circa 40 agenti di accertata tossicità/cancerogenicità, fra i quali: benzene, composti del cromo, formaldeide, arsenico, acrilonitrile, cadmio, piombo, tricloroetilene, 1,3 butadiene, cloruro di vinile, idrocarburi aromatici policiclici, materiale particolato (PM_{10}-$PM_{0,1}$), in particolare quello derivante dalle emissioni dei motori diesel[3].

Gli effetti tossici

Gli effetti tossici per l'uomo, dovuti all'esposizione ad inquinanti atmosferici, possono essere di tipo acuto, soprattutto per persone particolarmente suscettibili come bambini ed anziani, e/o cronici.

A) Effetti tossici acuti: possono manifestarsi a livello di vari organi ed apparati, in particolare quelli a diretto contatto con gli inquinanti, quali la cute e l'apparato respiratorio, ma anche a livello del sistema nervoso, rene ed apparato urinario, e del sistema immunitario. Le manifestazioni cliniche possono essere di vario tipo e dipendono principalmente dalla tipologia e concentrazione degli inquinanti, e dalla sensibilità individuale. Possono presentarsi come patologie infiammatorie delle vie respiratorie, o come patologie cardiocircolatorie con esiti a volte molto gravi. Studi epidemiologici hanno infatti dimostrato che un aumento della concentrazione di PM_{10} di 10 $\mu g/m^3$ può determinare un aumento della mortalità giornaliera dello 0,5%[4]. Un esempio paradigmatico fu l'episodio verificatosi a Londra nel 1952 durante il quale, in conseguenza di 5 giornate di forte smog, tra il dicembre '52 ed il febbraio '53, si verificarono oltre 12.000 decessi in più rispetto agli attesi[5]. In uno studio pubblicato recentemente, condotto in 95 grandi città americane (rappresentative del 40% della popolazione USA), è stato riportato che un incremento di 10 ppb di ozono nella settimana precedente, era associato ad un aumento dello 0,5% della mortalità giornaliera e, in specifico, ad un aumento dello 0,64% della mortalità per patologie cardiovascolari e polmonari[6].
B) Effetti tossici cronici: l'esposizione prolungata ad inquinanti atmosferici, in particolare $PM_{2,5}$, può determinare un aumento della mortalità per patologie cardiocircolatorie e tumorali. Uno studio condotto all'inizio degli anni '90 negli USA dimostrò come la sopravvivenza dei cittadini residenti in città a più basso livello di PM era maggiore di circa 2 anni rispetto a quella di coloro che vivevano in città con livelli di concentrazione di PM più elevata[7]. Questi dati sono confermati dai risultati di una più recente ricerca, sempre americana, dalla quale risulta che la mortalità per cancro del polmone aumenta dell'8% per ogni incremento di 10 $\mu g/m^3$ di $PM_{2,5}$[8].

Le prospettive

La consapevolezza della dimensione e dell'urgenza del problema ecologico e sanitario, dovuto all'inquinamento atmosferico delle grandi città e delle aree metropolitane, rende necessaria la promozione di una strategia di controllo che, a nostro avviso, schematicamente comporta 4 momenti, dei quali uno culturale e tre tecnologici.

Il momento culturale consiste nella promozione di una nuova antropologia che, in primo luogo, in linea con i dettami della strategia di sviluppo sostenibile ed emancipata dalla dipendenza dai miti del consumismo in generale (in specifico dall'immagine dell'automobile come *status symbol*), determini gradualmente una riduzione dell'autolocomozione.

I principali obiettivi che, nel breve periodo, l'innovazione tecnologica si deve proporre, al fine di diminuire l'impatto sanitario dell'inquinamento atmosferico, dovrebbero consistere in:

1) produzione di carburanti meno inquinanti, sia in termini di vapori che di composti generati durante la combustione;
2) messa a punto di motori più efficienti che consentano una riduzione dei prodotti di combustione emessi;
3) sistemi di abbattimento dei prodotti di combustione (come la post-combustione catalitica).

La produzione di carburanti meno inquinanti presuppone studi di ricerca biomedica per caratterizzare qualitativamente e quantitativamente effetti tossici a breve e a lungo termine (in particolare cancerogeni) dei vari tipi di carburanti, dei loro costituenti e dei loro prodotti di combustione, e soprattutto presuppone una valutazione relativa dei rischi, al fine di operare scelte più congrue che abbiano come risultato una riduzione di tali rischi.

I problemi della tipologia dei carburanti, dei motori e dei sistemi di abbattimento dei prodotti di combustione sono strettamente correlati ed interdipendenti, e vanno visti ed affrontati in maniera unitaria.

Nella situazione attuale le problematiche ecologiche e sanitarie correlate al binomio carburanti - motori, non possono e non devono essere gestite nell'ottica del solo profitto, storicamente datata, ma ancora prevalente. Le scelte dovranno essere fatte invece tenendo conto di valutazioni globali, che considerino sia i pro che i contro, e che abbiano una base scientifica adeguata.

Ad esempio, l'introduzione di nuovi combustibili può ridurre la presenza di alcuni componenti tossici per l'ambiente e per la salute, ma ne può generare, e di fatto ne genera, di nuovi. Rischio sconosciuto non significa assenza di rischi. Un nuovo combustibile non può essere presentato come migliorativo fino a quando ciò non sia stato dimostrato da studi adeguati.

Questa strategia presenta degli aspetti tecnologici, economici, sociali e sanitari ugualmente importanti e complessi. Bisogna però prendere atto che, rispetto all'attenzione che viene data alla ricerca scientifica ed agli investimenti finalizzati agli aspetti tecnologico-economici e sociologici, molte meno risorse sono destinate alla ricerca biomedica, vista ancora di retroguardia, e cioè riparativa dei guasti compiuti e non, come in realtà dovrebbe essere considerata, ricerca di sviluppo.

Il progetto di ricerca della Fondazione Ramazzini sui rischi cancerogeni dei carburanti, loro costituenti ed additivi: risultati ed indicazioni

Nonostante sia da tempo noto il problema dell'entità dell'impatto ambientale dei carburanti per autotrazione, le conoscenze scientifiche e le informazioni biomediche sui possibili rischi per la salute, in particolare cancerogeni, derivanti dall'esposizione a vapori e prodotti di combustione di tali composti, sono a tutt'oggi scarse, frammentarie, inadeguate e spesso frutto di iniziative non coordinate e contingenti. Infatti, le conoscenze finora acquisite non consentono, o consentono solo marginalmente, una valutazione quantitativa dei rischi per la salute dei vari tipi di carburanti.

È per questo motivo che, già a metà degli anni '70, presso il Centro di Ricerca sul Cancro della Fondazione Ramazzini, è iniziato un vasto progetto di ricerca integrato e sistematico per la valutazione dei possibili effetti cancerogeni di varie tipologie di carburanti, dei loro maggiori costituenti ed additivi.

La tipologia ed i risultati degli studi sperimentali di cancerogenicità a lungo termine condotti dalla Fondazione Ramazzini su vari tipi di carburanti, sui maggiori costituenti aromatici delle benzine e sui principali additivi delle benzine, sono riportati rispettivamente nelle Tabelle 1-3.

Questo progetto di ricerca, condotto nell'arco di oltre 20 anni, ha comportato complessivamente l'effettuazione di 51 saggi sperimentali, lo studio di 42 diversi composti, e l'utilizzo di oltre 20.000 animali da laboratorio (ratti e topi). Tutti gli esperimenti sono stati condotti secondo le Buone Pratiche di Laboratorio internazionali, e quindi i risultati sono fruibili per nuove scelte tecnologiche e per adeguamenti di normative.

In particolare, il progetto ha permesso di dimostrare per la prima volta che:

1) tutti i carburanti correntemente utilizzati sono in grado di indurre tumori negli animali sperimentali;

Tabella 1 - Studi di cancerogenicità a lungo termine su ratti Sprague-Dawley, esposti a vari tipi di carburanti, condotti dalla Fondazione Ramazzini. Risultati

Agente	Cancerogenicità[a]
Benzina con piombo[9]	+
Benzina senza piombo con alto contenuto di aromatici (tipo europeo)[9]	+
Benzina senza piombo a basso contenuto di aromatici (tipo americano)	+
Diesel[9]	+
Cherosene[9]	+

[a] + = chiara evidenza

Tabella 2 - Studi di cancerogenicità a lungo termine su roditori, esposti a vari tipi di costituenti aromatici presenti nelle benzine, condotti dalla Fondazione Ramazzini. Risultati

Agente	Tumori maligni totali/ 100 animali (M + F)	Indice di cancerogenicità[a]
Benzene[10]	160,8	6,56
Toluene[11]	68,8	2,81
Xileni[9]	56,4	2,30
Etilbenzene[9]	40,3	1,64
Olio di oliva (controllo)	24,5	1,00

[a] Rapporto tra i tumori maligni totali osservati e quelli attesi

Tabella 3 - Studi di cancerogenicità a lungo termine su roditori, esposti a vari tipi di ottimizzatori di ottani delle benzine, condotti dalla Fondazione Ramazzini. Risultati

Agente	Cancerogenicità[a]	
	Ratto	Topo
Additivi ossigenati		
Alcool metilico[12]	+	
Alcool etilico[12]	+	+
MTBE[13]	+	
ETBE[14]	(+)	
TAME[15]	(+)	
DIPE[15]	+	
Isoparaffine		
TMP	(+)	

[a] + = chiara evidenza; (+) = limitata evidenza

2) il benzene è un agente cancerogeno multipotente e, proprio a seguito di questa dimostrazione, sono seguite a livello nazionale ed internazionale normative più restrittive per quanto riguarda l'esposizione negli ambienti di lavoro e di vita generale;
3) l'MTBE (etere metilterbutilico), prodotto al mondo in oltre 20 milioni di tonnellate, e che negli anni '90 ha sostituito il piombo come ottimizzatore di ottani della benzina (la quale per questo motivo fu definita "verde"), è un composto che produce linfomi e leucemie in ratti femmine, e tumori del testicolo nei maschi; e
4) altri additivi ossigenati, ritenuti attualmente potenziali alternative all'MTBE, risultano cancerogeni.

I risultati di queste ricerche indicano la necessità di identificare e produrre nuove tipologie di carburante di origine fossile, le cui formulazioni contengano meno sostanze tossiche o, perlomeno, a minor concentrazione rispetto alle attuali.

Nel lungo periodo soluzioni finalizzate alla riduzione della mobilità privata ed allo sviluppo di infrastrutture per la mobilità su mezzi pubblici non sono più procrastinabili.

Nel frattempo, i dati epidemiologici sugli effetti tossici acuti dell'inquinamento atmosferico riportati nella letteratura scientifica nazionale ed internazionale, richiamano la necessità di misure precauzionali[16, 17]. Fra queste la sospensione del traffico urbano nelle giornate di elevata concentrazione di PM, trova una motivata giustificazione.

Conclusioni: il ruolo della ricerca scientifica

La salvaguardia dell'ambiente, la tutela della salute e della qualità della vita rappresentano un problema planetario, e sono un tutt'uno per una strategia che voglia perseguire un modello di sviluppo più fisiologico, finalizzato ad una maggiore conservazione delle risorse, e ad una più equa risposta alle legittime aspettative di tutta la popolazione del globo.

È certamente vero che molti errori sono stati commessi, molti disastri sono stati compiuti, e per questo c'è disorientamento nella società di oggi.

Per uscire da tale situazione è innanzitutto necessario censire le risorse, censire i ritmi di ricostituzione di quelle rigenerabili, prevedere l'aumento della domanda di beni puntando soprattutto sulla loro qualità e sulla loro essenzialità. Bisogna inoltre demolire i miti artificiosi del consumo, che trasforma risorse preziose in rifiuti tossici e materie prime in scorie e quindi, in definitiva, emanciparsi dai condizionamenti psicologici.

La ricerca scientifica non è certamente sufficiente a determinare questo capovolgimento, ma è necessaria. Essa però dev'essere libera nell'identificare le problematiche, nel definire le priorità, nel decidere i programmi, nel valutare i risultati conseguiti e, soprattutto, deve stabilire dei rapporti con la società, che deve avvalersi del suo contributo. Tali rapporti tuttavia non devono ledere l'autonomia della ricerca scientifica: in altre parole, devono essere rapporti di interazione ed interdipendenza, ma non di dipendenza.

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Eur. J. Oncol., vol. 10, n. 1, pp. 37-43, 2005

Il trattamento dei pazienti oncologici in fase cachettica

The treatment of oncological patients in the cachectic phase

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Riassunto

La sindrome dell'anoressia-cachessia correlata al cancro (cancer anorexia-cachexia syndrome = CACS) è una combinazione di anoressia, distruzione tissutale, perdita di peso e scadimento del *performance status*. Essa rappresenta la più frequente e grave sindrome paraneoplastica del paziente con malattia in fase avanzata. Le alterazioni metaboliche alla base di questa sindrome giustificano il ridotto introito calorico e l'aumento della spesa energetica. Esse sono il risultato dell'azione di fattori circolanti in parte prodotti dal tumore, in parte dalle cellule dell'ospite, principalmente i macrofagi, in risposta al tumore. L'obiettivo terapeutico generale nei pazienti con CACS dovrebbe tendere a prevenire l'insorgenza dei sintomi. Nell'ambito della terapia farmacologica sono stati studiati diversi farmaci, alcuni validati da numerosi *trials*, altri tuttora in fase di sperimentazione. Nel trattamento a lungo termine di questa sindrome, diversi studi hanno evidenziato il ruolo centrale dei progestinici (medrossiprogesterone acetato e megestrolo acetato), anche se ulteriori studi sono necessari per meglio chiarire il reale effetto anabolizzante di queste sostanze e il possibile vantaggio di terapie di combinazione con nuovi farmaci. Inoltre gli studi futuri dovrebbero essere rivolti alle molecole in grado di interferire con i meccanismi patogenetici coinvolti nella CACS e ad identificare biomarcatori i cui livelli siano alterati in corso di CACS. Il loro dosaggio, affiancato alla valutazione clinica dei pazienti, potrebbe consentire di individuare precocemente i pazienti in cui i sintomi non sono ancora evidenti. Eur. J. Oncol., 10 (1), 37-43, 2005

Parole chiave: **cachessia neoplastica, trattamento**

Summary

Cancer anorexia-cachexia syndrome (CACS) is a combination of anorexia, tissue wasting, weight loss and poor performance status. It is the most frequent and lifethreatening paraneoplastic syndrome in advanced cancer patients. Metabolic alterations that lead to this syndrome justify a decreased food intake and an increased energy consumption. These alterations depend on circulating factors released by tumour cells and/or by host immune cells, especially macrophages, in response to the tumour. Therapeutic interventions in CACS patients might be addressed to avoid symptoms onset. Among drug therapy many agents have been studied, some of them validated by clinical trials and some others actually part of ongoing studies. Many trials demonstrated the central rôle of progestational drugs (medroxyprogesterone acetate and megestrol acetate) in the long-term treatment of CACS patients, but further studies are mandatory to better clarify the true anabolic effect of these agents and whether there is any advantage in combining them with other drugs. Future studies might be addressed to clarify the rôle of molecules that interfere with CACS metabolic pathways and to identify biomarkers with serum level alterations in CACS patients. The dosage of these markers, associated with the clinical evaluation, could be helpful in identifying patients before symptoms onset. Eur. J. Oncol., 10 (1), 37-43, 2005

Key words: **neoplastic cachexia, treatment**

Received/Pervenuto 18.11.2004 - Accepted/Accettato 10.12.2004
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Fisiopatologia della sindrome da anoressia-cachessia neoplastica

La sindrome dell'anoressia-cachessia correlata al cancro (cancer anorexia-cachexia syndrome = CACS), rappresenta, indipendentemente dall'istologia e dalla localizzazione del tumore primitivo, la più frequente sindrome paraneoplastica nei pazienti affetti da cancro in fase avanzata[1, 2]. Oltre il 50% dei pazienti affetti da neoplasia, soprattutto nelle fasi avanzate, sviluppa i segni e i sintomi della cachessia e circa il 20% muore per le conseguenze della malnutrizione[3]. Nei pazienti con malattia in fase avanzata esiste una correlazione fra l'entità della perdita di peso e la sopravvivenza[4]. La CACS può essere definita come un circolo vizioso di anoressia, distruzione tissutale, perdita di peso e scadimento del *performance status*, deplezione delle scorte proteiche, lipidiche e di carboidrati. Spesso coesistono astenia, anemia, nausea e vomito, perdita del rispetto di sé e della propria immagine. In questi pazienti si osserva inoltre un'aumentata sensibilità alle infezioni e una ridotta tolleranza ai trattamenti antiblastici. Correlata con la CACS è la cosiddetta *fatigue,* sindrome multifattoriale presente in oltre il 60% dei pazienti neoplastici, caratterizzata da stato di affaticabilità sproporzionato all'esecuzione delle normali attività quotidiane, associato a ridotta capacità di reazione psicologica alla fatica. Appare difficile stabilire quanto essa sia dipendente dalla CACS, dall'anemia o da altri fattori[5].

La patogenesi della CACS è multifattoriale[6, 7] e va ricondotta ad alterazioni di tutti i sistemi metabolici, produzione di citochine proinfiammatorie e di fattori circolanti di derivazione tumorale, ridotto introito calorico, aumento della spesa energetica e, probabilmente, ad altri fattori ancora sconosciuti. L'aumento della spesa energetica nella CACS è legato ad alterazioni del metabolismo glucidico, proteico e lipidico. Si assiste infatti all'attivazione di cicli futili come il ciclo di Cori e alla gluconeogenesi a partire da lattato, aminoacidi muscolari e acidi grassi liberi con perdita delle riserve proteiche e lipidiche. L'aumentato *turnover* del glucosio si associa a intolleranza glucidica e insulinoresistenza, mentre il *turnover* proteico si associa ad incremento della gluconeogenesi, riduzione della sintesi proteica muscolare ed epatica, aumento della sintesi epatica di proteine della fase acuta, aumento dei livelli sierici di fattore inducente la proteolisi (proteolysis inducing factor = PIF). Il PIF è un proteoglicano di 24 kd che aumenta la degradazione proteica muscolare attraverso la stimolazione della via ATP-ubiquitina-proteasomi. Nell'ambito del metabolismo lipidico si osserva un aumento della beta ossidazione degli acidi grassi e del *turnover* degli acidi grassi liberi, un aumento della lipoproteinlipasi sierica, ipertrigliceridemia e la produzione del fattore mobilizzante i lipidi (lipid mobilizing factor = LMF), che induce lipolisi attraverso l'attivazione dell'adenilatociclasi.

Alcuni "effetti sistemici" della CACS quali anoressia, *fatigue*, febbre e turbe del metabolismo basale sono il risultato dell'azione di fattori circolanti in parte prodotti dal tumore, in parte dalle cellule dell'ospite, principalmente i macrofagi, in risposta al tumore. Fra essi un ruolo centrale è dato dalle citochine proinfiammatorie (IL-1, IL-6, TNF-alfa, IFN-gamma), le quali attivano la risposta di fase acuta con ridotta sintesi di proteine nobili (albumina, prealbumina e transferrina), aumentata sintesi di proteina C reattiva (C reactive proteine = CRP), aptoglobina e ceruloplasmina, aumento del *turnover* degli acidi grassi e della proteolisi. Al contrario citochine antinfiammatorie come IL-4 e IL-10 sembrerebbero possedere proprietà anticachettiche: la genesi di CACS potrebbe essere legata al bilancio fra questi due gruppi di citochine.

Recentemente, per spiegare l'anoressia presente nella CACS[7], sono state invocate alterazioni a livello ipotalamico mediate dall'azione delle citochine proinfiammatorie (incremento dei livelli di serotonina, disregolazione del circuito leptina/grelina, riduzione dei livelli ipotalamici di neuropeptide Y). In particolare, è oggi noto che la leptina, ormone secreto dal tessuto adiposo, è fondamentale nel meccanismo omeostatico di controllo del peso corporeo. Infatti, la perdita di peso determina una proporzionale riduzione dei livelli sierici di leptina, che induce a livello ipotalamico segnali oressigeni. Il neuropeptide Y è il più potente oressigeno ipotalamico e alterazioni dei suoi livelli sierici sono state associate con elevati livelli di alcune citochine infiammatorie, particolarmente IL-1.

Il trattamento nutrizionale

Il supporto nutrizionale (integratori alimentari, supplementi calorico-proteici, nutrizione artificiale) è stato ampiamente utilizzato, ma è ormai evidente che solo una minoranza dei pazienti può beneficiare di questo approccio con un reale impatto sulla sopravvivenza e sulla qualità della vita[4]. La nutrizione enterale è generalmente preferibile a quella parenterale in quanto consente di mantenere la normale flora microbica intestinale e le funzioni del sistema immunitario[8]; inoltre la nutrizione parenterale non determina un aumento della massa magra e si associa ad un aumentato rischio di complicanze infettive. L'impiego della nutrizione artificiale dovrebbe essere limitato ai pazienti incapaci di assumere sostanze per os ed evitato nei pazienti con un indice di Karnofsky inferiore a 50% o con

un'aspettativa di vita inferiore a 2 mesi[9]. A nostro parere è auspicabile un trattamento personalizzato che tenga presenti anche le aspettative del paziente, dal momento che non è sempre facile la valutazione prognostica in pazienti con malattia in fase avanzata.

Recentemente è stato proposto l'impiego di sostanze in grado di modulare le vie metaboliche coinvolte nella perdita di peso e nella resistenza alle terapie nutrizionali (aminoacidi quali arginina e glutamina, acidi grassi polinsaturi n-3 PUFA) o in grado di inibire *in vitro* la produzione di citochine pro-infiammatorie e il rilascio di PIF (acido eicosapentanoico o EPA)[10].

Metodi di valutazione dello stato nutrizionale

L'obiettivo terapeutico generale nei pazienti con CACS dovrebbe tendere a prevenire l'insorgenza dei sintomi, individuando precocemente i pazienti in cui i sintomi non sono ancora evidenti. Esistono diversi metodi (Tabella 1) per la valutazione clinica del paziente affetto da cachessia; tuttavia, mentre alcuni di essi vengono utilizzati routinariamente (peso corporeo, scala visivo-analogica per l'appetito), altri necessitano di ulteriore validazione. Il peso corporeo è un parametro quantitativo le cui limitazioni sono rappresentate da assenza di valore soglia di incremento significativo (> 0,5 kg?) e difficoltà a discriminare il possibile effetto sodio-ritentivo. Al contrario, l'appetito può essere misurato in maniera quantitativa (es. test di Corli) o qualitativa mediante VAS (scale analogico-visive, come QLQ-C30 o FAACT-AN), riproducibili e ampiamente validate. Le misurazioni antropometriche sono soggette a imprecisioni e non utilizzabili nella pratica clinica, mentre i metodi di valutazione della massa magra non sono clinicamente riproducibili (diluizione del deuterio) o non possiedono valori standard per i pazienti malnutriti (impedenziometria). Negli studi futuri sarebbe auspicabile associare ai metodi tradizionali di valutazione dello stato nutrizionale anche il dosaggio dei biomarcatori circolanti, dal momento che una migliore conoscenza del ruolo delle varie citochine nei processi catabolici della CACS garantirebbe la possibilità di sviluppare strategie terapeutiche atte a prevenirli.

Trattamento farmacologico generale

Nell'ambito della terapia farmacologica, è stato recentemente evidenziato che i farmaci procinetici, come la metoclopramide, tradizionalmente impiegati come antiemetici, possono migliorare l'anoressia e ridurre il senso di sazietà precoce dei pazienti con malattia avanzata[11].

Uno studio pilota sugli antidepressivi ha dimostrato un modesto vantaggio a favore della mirtazapina (15-30 mg/die) nella riduzione di nausea, ansia, insonnia e anoressia dopo sette settimane di trattamento[12].

L'uso degli steroidi anabolizzanti, come il nandrolone decanoato, impiegati nella terapia della CACS per il loro effetto anabolizzante proteico, è attualmente fortemente limitato dai possibili effetti collaterali (danno epatico ed effetti endocrini).

Più di recente è stato proposto l'impiego dei corticosteroidi, ma gli studi condotti hanno dimostrato solo un beneficio a breve termine sull'appetito e sulla cenestesi, a fronte di numerosi effetti collaterali[13, 14]; pertanto sono indicati in pazienti con neoplasie avanzate e ridotta aspettativa di vita.

Fra i farmaci impiegati nel trattamento della CACS alcuni Autori menzionano:

- *cannabinoidi:* un recente studio randomizzato ha dimostrato però la superiorità del megestrolo acetato rispetto al dronabinolo nella palliazione dell'anoressia mentre la combinazione non sembra dare un vantaggio[15];
- *idrazina:* è stata studiata sulla base di un ipotetico effetto inibitorio sulla gluconeogenesi, ma non è stato dimostrato un vantaggio in termini di aumento del

Tabella 1 - Vantaggi e limiti delle varie metodiche di valutazione dello stato nutrizionale

Metodo	Strumenti	Utilità pratica	Limitazioni
Peso corporeo	Bilancia	Sì	Incremento minimo (>0,5 kg?) Effetto della ritenzione idrica
Appetito e qualità della vita	Scale analogiche (VAS) Questionari	Sì	-
Inchiesta dietetica	Tabelle nutrizionali	No	Difficile elaborazione
Misurazioni antropometriche	Plicometria	No	Imprecisione
Massa magra	Impedenziometria	Sì/No	Mancanza di standard per pazienti denutriti
Biomarcatori	Livelli plasmatici (IL2, IL6, TNF, ecc.)	Sì/No	Valori normali?

peso corporeo a fronte di una tossicità significativa e un peggioramento della qualità della vita[16];
- *melatonina:* alcuni studi hanno dimostrato una stabilizzazione del peso corporeo e una riduzione dei livelli circolanti di citochine proinfiammatorie (TNF-alfa); un recente studio randomizzato ha dimostrato un vantaggio statisticamente significativo su anoressia, cachessia ed astenia della combinazione melatonina (20 mg/die) e terapia di supporto verso la sola terapia di supporto[17];
- *talidomide:* recentemente impiegata come antiangiogenetico in alcuni tipi di tumore, ha anche un'azione anticachettica per la sua capacità di inibire la sintesi di TNF-alfa; Bruera *et al* hanno dimostrato una riduzione dell'insonnia, della nausea ed un miglioramento dell'appetito e del senso di benessere con la somministrazione di talidomide 100 mg/die[18];
- *ATP:* in uno studio clinico randomizzato in pazienti con neoplasia polmonare non a piccole cellule, l'infusione endovenosa di ATP ha determinato una stabilizzazione del peso corporeo nei pazienti trattati rispetto ai controlli[19];
- *COX-2 inibitori:* le prostaglandine prodotte dalle COX-2 possono svolgere un ruolo importante nello sviluppo del cancro attraverso la stimolazione della crescita tumorale e della neoangiogenesi; studi preclinici dimostrano un ruolo antiangiogenetico e proapoptotico degli inibitori delle COX-2 su linee cellulari di carcinomi umani trapiantati nel topo[20]; Davis *et al* hanno dimostrato un effetto anticachettico di celecoxib (inibitore selettivo delle COX-2) in modelli animali[21];
- *acido eicosapentanoico (EPA):* uno studio randomizzato in doppio cieco placebo-controllato non ha dimostrato un vantaggio in termini di aumento di peso ed appetito[22];
- *eritropoietina (EPO):* l'uso di α-epoetina in associazione a indometacina ha dimostrato un vantaggio statisticamente significativo su aumento del peso corporeo e metabolismo basale rispetto alla sola indometacina in pazienti con neoplasia avanzata e calo ponderale >10%[23].

Trattamento con progestinici ad alte dosi

L'esperienza condotta nella prima metà degli anni 80 con le alte dosi (> 500 mg al giorno per via intramuscolare o per os) di medrossiprogesterone acetato (MPA) nel trattamento delle pazienti con carcinoma della mammella in stadio avanzato, ha dimostrato un incremento del peso corporeo nel 50% delle pazienti trattate, associato a miglioramento dell'appetito e del *performance status* (PS). Da ciò si è desunto che le alte dosi di MPA avessero un effetto anabolizzante paragonabile a quello osservato con i derivati del testosterone. Tuttavia emersero alcuni quesiti: anzitutto, se l'aumento del peso corporeo fosse correlato o indipendente dall'azione antitumorale del MPA; inoltre, se si trattasse di un effetto anabolizzante vero o di tipo steroideo; infine, quanto fosse implicata la ritenzione idrica nell'aumento del peso corporeo.

La risposta alla prima domanda si evince dai risultati di uno studio clinico controllato coinvolgente 65 pazienti affetti da neoplasie non ormono-sensibili, sottoposti a trattamento con 2000 mg/die di MPA. Tale studio ha dimostrato un aumento dell'appetito nel 62% e un incremento del peso corporeo >0,5 kg nel 63% dei pazienti[24].

Allo scopo di dimostrare l'effetto anabolizzante "vero", un gruppo di dieci pazienti affetti da neoplasie avanzate non ormono-sensibili è stato trattato con alte dosi di MPA (>500 mg/die po o im). Prima e dopo il trattamento sono stati registrati parametri antropometrici (peso corporeo, plicometria, forza muscolare) e parametri metabolici (introduzione calorica e proteica attraverso sorveglianza dietetica, escrezione urinaria di azoto misurata con il metodo di Kieldahl e bilancio azotato). Tale studio[25] ha evidenziato un significativo incremento nel bilancio dell'azoto e nell'introduzione calorica e proteica, senza significativo incremento dei parametri antropometrici fatta eccezione per la forza muscolare (24,4 kg prima, 29,1 dopo, $p<0,02$).

Infine, in un altro studio condotto su 10 pazienti affetti da neoplasia in fase avanzata, non è stata individuata nessuna azione sul metabolismo salino e dell'acqua[26]. Ulteriori studi hanno inoltre dimostrato una ridotta sintesi e rilascio di citochine pro-infiammatorie nei pazienti trattati, confermando un effetto anti-cachettico del MPA[27]. Il trattamento con alte dosi di progestinici è ben tollerato e gli effetti collaterali severi sono di rara incidenza. L'insorgenza di fenomeni tromboembolici è stata osservata soltanto con la somministrazione per via intramuscolare. La terapia con MPA è controindicata solo in caso di diabete, severo danno epatico, stato di ipercoagulabilità o grave ipertensione[25, 28]. La dose raccomandata è 1000 mg/die per os (equivalente a 160 mg di megestrolo acetato), oppure 500-1000 mg im alla settimana nei pazienti non in grado di assumere terapia per os. Un possibile vantaggio dell'impiego del MPA rispetto al megestrolo è la disponibilità di una formulazione im depot che consente la somministrazione anche ai pazienti meno complianti garantendo il mantenimento di adeguati livelli plasmatici.

Gli effetti del trattamento con MPA su anoressia e peso corporeo sono stati oggetto di studi clinici controllati

Tabella 2 - Studi randomizzati sul medrossiprogesterone acetato

	N. pazienti	Dose MPA	Risultati		
			Anoressia	Peso	Altri parametri
Downer *et al*[29]	60	300 mg/d po	p = 0,015	p<0,05	–
Kornek *et al*[30]	31	500 mg/d po	60% *vs* 43%	+ 3 kg p = 0,06	Miglioramento qualità di vita (40% *vs* 14%, NS)
Neri *et al*[31]	279	1000 mg/d po	-	p = 0,001	Miglioramento PS
Simons *et al*[32]	206	1000 mg/d po	p = 0,01	+ 0,6 kg (p = 0,04)	Energia: p = 0,01 Metabolismo basale: p = 0,009

con placebo[29-32] (Tabella 2), che hanno confermato un miglioramento di entrambi i parametri.

È importante sottolineare che in 3 studi[29, 31, 33], la somministrazione di MPA durante la chemioterapia ha determinato un miglioramento della qualità della vita. In contrasto con le nostre esperienze precedenti, alcuni Autori[32] hanno dimostrato che l'aumento del peso corporeo coinvolge la massa grassa mentre la massa magra non è significativamente influenzata dal trattamento con MPA.

A partire dal 1997 è stato introdotto con successo nel trattamento anabolizzante della CACS un altro progestinico, il megestrolo acetato (MA)[34]. Gli studi clinici condotti con MA *vs* placebo, sia a basse dosi (160 mg/die) che a dosi più alte (>320 mg/die)[35], hanno evidenziato un miglioramento dei sintomi, valutato mediante scale visivo-analogiche, nei pazienti trattati con MA rispetto ai trattati con placebo, in assenza di significative modificazioni dello stato nutrizionale, suggerendo che possano esserci ulteriori effetti al di là del semplice aumento di peso[36].

Conclusioni

La CACS è il risultato di una complessa interazione di alterazioni metaboliche provocate da fattori circolanti tumorali e da citochine (CK). Il quadro clinico dei singoli pazienti è ulteriormente complicato da fattori individuali, quali le comorbidità e aspetti psicologici. Individuare una terapia standard è particolarmente difficile, tuttavia, anche sulla base di recenti revisioni sistematiche[37], diamo alcune indicazioni per il trattamento (Tabella 3):

– i progestinici devono essere somministrati in pazienti con aspettativa di vita superiore alle 4 settimane;
– l'uso di procinetici (metoclopramide) è raccomandato soprattutto nei pazienti in terapia con oppioidi;
– i corticosteroidi vanno utilizzati per brevi periodi, eccetto nei pazienti con metastasi cerebrali, coinvolgimento mediastinico, sindromi dolorose.

Tabella 3 - Riepilogo dei farmaci impiegati nella CACS

	Meccanismi d'azione	Efficacia	Livello evidenza
Progestinici	Stimolazione appetito, <CK	Sì	A-B1
Corticosteroidi	Stimolazione appetito, <CK	Sì	B1
Melatonina	<CK	Sì	B2
Talidomide	<CK	Sì	C
Inibitori COX-2	<CK, <PIF	Sì	C
EPO	?	Sì	C
Anabolizzanti	Stimolazione appetito	No	C
Cannabinoidi	Stimolazione appetito	No	C
Antidepressivi	Stimolazione appetito	No	C
Procinetici	Procinetico	No	C
EPA	<CK, <PIF	No	B2

Diversi nuovi farmaci sono attualmente oggetto di studi clinici controllati. Si tratta di farmaci che interferiscono nel meccanismo patogenetico della CACS a diversi livelli, stimolando l'appetito a livello centrale, interferendo nei livelli circolanti delle citochine, dei fattori proteolitici e lipolitici tumorali e nel catabolismo muscolare. La disponibilità di farmaci che agiscono a diversi livelli nel processo patogenetico della CACS fornisce la possibilità di terapie di combinazione. A tal proposito, in un recente studio pilota condotto su 15 pazienti affetti da adenocarcinoma polmonare con calo ponderale ed anoressia, mediante trattamento con MPA 1000 mg/die e celecoxib 400 mg/die, si è ottenuto un importante aumento di peso ed appetito[38]. Recentemente, abbiamo attivato uno studio osservazionale che prevede il trattamento di pazienti cachettici e con anemia concomitante con MPA (1000 mg/die) in associazione a darbepoetina (150 μg sc/1 volta alla settimana). Oltre alla valutazione della qualità della vita, dell'appetito e del peso corporeo, è prevista anche la misurazione delle variazioni di composizione corporea e dei livelli di citochine.

I futuri studi dovrebbero essere rivolti alla individuazione di terapie di associazione e a meglio definire i parametri adeguati ad individuare precocemente i pazienti che sono a rischio di manifestare clinicamente la sindro-

me prima che i sintomi siano evidenti. Inoltre, poiché la CACS è una sindrome multifattoriale, sarebbe opportuno riuscire a meglio caratterizzare per ciascun paziente il contributo prevalente dei singoli sintomi (anoressia o astenia) per identificare una terapia più efficace e personalizzata.

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Eur. J. Oncol., vol. 10, n. 1, pp. 45-54, 2005

Liver metastases from colorectal cancer

Metastasi epatiche da carcinoma colorettale

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Summary

The liver is the main target organ for colorectal cancer (CRC) metastases. About 50% of all patients affected by CRC develop liver metastases. Surgery remains the only potentially curative strategy, but indications to surgery and resectability criteria are now less restrictive than before so that a more aggressive approach in the treatment of metastatic lesions is the rule. However in spite of these increasing indications surgery is not possible in the majority of patients. For non resectable patients two options are available: local treatment strategies (intra-arterial infusion chemotherapy or radiofrequency ablation and cryosurgery alone or in combination with surgery) and systemic chemotherapy. Locoregional treatments are efficacious in obtaining objective responses, but they are expensive, not easy to manage, and are still accompanied by important side effects; for these reasons, their use is necessarily limited to centres with a good granding in these techniques. On the contrary, the new schedules of systemic infusion therapy, achieved with fluorouracil (5-FU), oxaliplatin (OHP) and irinotecan (CPT-11) are well tolerated and have high rates of objective response, enabling initially unresectable patients to undergo surgery, with a 5-year survival rate comparable to that observed for primary resectable patients. Therefore chemotherapy no longer has only a palliative aim, but becomes a fundamental moment of a combined medical and surgical treatment with curative purpose. After surgery, two-

Riassunto

Il fegato è il principale organo bersaglio di metastasi da cancro del colon-retto (CCR). Circa il 50% dei pazienti affetti da CCR è destinato a sviluppare metastasi epatiche nel corso della malattia. La chirurgia rimane ad oggi l'unico trattamento potenzialmente curativo. Le indicazioni alla chirurgia e i criteri di resecabilità sono ora meno rigidi che in passato ed un atteggiamento più aggressivo nel trattamento delle lesioni metastatiche è la regola. Però, nonostante l'allargamento delle indicazioni, la chirurgia non è possibile nella maggior parte dei pazienti. Per questi casi rimangono due opzioni terapeutiche: i trattamenti locoregionali (chemioterapia intraarteriosa oppure ablazione con radiofrequenza e criochirurgia da sola o in combinazione con la chirurgia) e la chemioterapia sistemica. I trattamenti locoregionali sono molto efficaci nell'indurre risposte obiettive, ma sono costosi, non semplici da gestire, ancora gravati da effetti collaterali importanti, sicchè le loro applicazioni sono necessariamente limitate a centri con esperienza in tale tipo di terapia. Al contrario, i nuovi schemi di terapia infusionale sistemica a base di 5-fluorouracile (5-FU), oxaliplatino (OHP) e irinotecan (CPT-11) sono ben tollerati e hanno dimostrato efficacia. Tali regimi terapeutici rendono possibile la chirurgia per pazienti inizialmente non resecabili. Questi pazienti hanno una probabilità di sopravvivenza a 5 anni simile a quella dei pazienti operabili alla diagnosi. Quindi la chemioterapia non ha più solo uno scopo palliativo, ma diviene il momento fondamentale di una strategia com-

Received/Pervenuto 27.10.2004 - Accepted/Accettato 21.12.2004
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thirds of patients relapse in the first two years, so that adjuvant therapy has been investigated to reduce recurrence rates, mainly by testing hepatic arterial infusion (HAI) schedules. Unfortunately, no randomized trials have yet been published on the rôle of systemic intravenous adjuvant chemotherapy which could be useful in clinical practice. Finally, we report the results of our monoinstitutional experience, suggesting a possible rôle of systemic adjuvant chemo-therapy in reducing recurrence rates after liver meta-stasectomy. Probably, in the next few years, new targeted drugs and locoregional therapies will contribute to further improve prognosis of such patients, in neoadjuvant, adjuvant and palliative settings. Eur. J. Oncol., 10 (1), 45-54, 2004

***Key words*: colorectal cancer, liver metastases, 5-fluorouracil, oxaliplatin, irinotecan**

binata medica e chirurgica con intento curativo. Dopo la chirurgia recidivano circa i due terzi dei pazienti nell'arco dei primi due anni; per questo motivo è stata sperimentata la chemioterapia adiuvante, finora testando principalmente protocolli di chemioterapia intraarteriosa. Purtroppo però ancora oggi non sono stati pubblicati studi randomizzati sul ruolo della chemioterapia sistemica intravenosa adiuvante utilizzabili nella pratica clinica. Infine, riferiamo i risultati dell'esperienza del nostro istituto, che suggeriscono un possibile ruolo della chemioterapia sistemica adiuvante nella riduzione dei tassi di recidiva dopo la metastasectomia epatica. Probabilmente, nei prossimi anni i nuovi farmaci mirati e i progressi nelle terapie locoregionali contribuiranno a migliorare ulteriormente la prognosi di questi pazienti, in ambito neoadiuvante, adiuvante e palliativo. Eur. J. Oncol., 10 (1), 45-54, 2004

***Parole chiave*: cancro colorettale, metastasi epatiche, 5-fluorouracile, oxaliplatino, irinotecan**

Introduction

The treatment of liver metastases of colorectal cancer (CRC) represents one of the main controversial points in oncology. The liver is the main target organ for CRC metastases. This kind of cancer is the third leading cause, by frequency, of tumour-related death in Western countries after lung and breast cancer. Around 50% of CRC patients in phase III and 20% of those in phase II are destined to develop liver metastases. Overall, including patients who are diagnosed in advanced stages, liver metastases develop in 50% of all cases. Around 20-40% of resected patients with liver metastases are still alive at 5 years[1]. As a consequence, the importance of an optimal treatment of this pathology, for which the collaboration between the oncologist, the surgeon and the radiologist represents the best therapeutical strategy available, becomes evident. New drugs and agents, new surgical techniques, and new local treatment strategies are available, but agreement on the best choice of treatment is still to be reached. In this article, presented as a decisional flow-chart, the main problems and achievements on this topic are analysed.

The natural history of liver metastases

A few studies can allow us to determine the natural history of liver metastases in the absence of treatment. The median survival period for untreated patients rarely goes beyond 9 months. In a prospective study, conducted between 1980 and 1990 on 484 consecutive patients with non-treated liver metastases, the median survival rate was 31% at 1 year, 7.9% at 2 years, 2.6% at 3 years, and 0.9% at 4 years. The independent factors that influenced the survival rate were: the volume of liver involvement, the presence of extra-hepatic disease, metastatic lymph nodes in the mesentery, the carcino-embryonic antigen (CEA) level, and the patient's age. Depending on the presence or absence of these factors, the survival period varied between 3 and 21 months[2]. Only a few retrospective studies actually compare the outcome of patients with potentially resectable but untreated lesions, with that of patients who have undergone surgery: one study compared two groups of patients with a single liver metastasis, and discovered a median overall survival (OS) of 36 months for those who were operated, against a median OS of 19 months for those not operated[3]. Nevertheless, these retrospective studies display a weakness in that those patients who cannot undergo surgery represent a subset of all patients, and, additionally, one with a rather unfavourable prognosis; patients for whom surgery is possible, instead, have, as a group, a more positive prognosis. It has been ascertained, in fact, that surgery represents the only potentially curative form of treatment for this group of patients, representing the only hope of long-term survival. Liver transplantation has been abandoned because subsequent immunosuppression was related to relapse in all patients[4].

Surgical criteria

It is therefore necessary to direct the patient who can be operated to surgery. The criteria for resectability are therefore of paramount importance.

Judgement on resectability varies according to many factors: some are technical, usually dependent on the extension of liver involvement and on the type of structures affected; others depend on the general conditions of the patient. Generally accepted controindications to surgery are: multiple bilobar, or ill-located metastases involving large hepatic vessels (portal vein, hepatic artery and vena cava/sovrahepatic), portal thrombosis, extrahepatic disease.

In the resectability evaluation, we must therefore consider several fundamental points, covering the technical aspects and the oncological radicality as much as the patient's general conditions. Having checked for the absence of extra-hepatic disease, for the absence of comorbidity and of any other condition that may rule out surgery, we can move on to evaluate the resectability limit: if there are no oncological contraindications (technical aspects), we must keep in mind that a sufficient quantity of normal liver parenchyma must be present after the resection in order to avoid post-surgery liver failure. In the absence of liver disease, up to 75% of the liver parenchyma can be removed without inducing post-operative liver failure. It appears that pre-surgery chemotherapy does not increase the mortality or morbidity rates.

Further, we must rule out the existence of non-resectable extra-hepatic disease. The presence of extra-hepatic disease does not automatically rule out surgery, since in selected cases there could be factors pointing to resections of liver and lung metastases, simultaneously or during separate interventions: long-term survival is reported in a significant number of patients when complete resection of extrahepatic disease is carried out, especially in case of lung metastases[5, 6]. New surgical techniques, like pre-operative portal vein embolization or two-stage hepatectomy, enable larger resections of the liver parenchyma, without the risk of post-operative liver failure, and make it possible, in selected cases, to remove bilobar multinodular disease, giving a possibility of long-term survival[7].

It is therefore clear how each of the aforementioned points are the result of subjective judgement and evaluations, regarding both the oncological aspects and the general evaluation of the patient: the judgement on comorbidity is also subjective and the resectability criteria (technical factors) are the result of the technical capabilities and the experience of the surgical team.

Some years ago an international symposium on liver metastases was held in Bologna. Several surgeons coming from all over the world attended this 3-day discussion. At the end of the meeting, the final statement was: "...the indications for surgery are less restrictive with some surgeons saying there are no limits".

In conclusion, although a series of universally-recognized factors and criteria do exist, the final evaluation is always subjective and depends on the experience and the capabilities of each individual centre: it is, therefore, almost impossible to establish definite limits.

The purpose of surgery is to reach the oncological radicality (R0 resection), i.e. the removal of all lesions with a margin of at least 1 cm. This margin is the most important factor in the prognosis. The type of resection (wedge or anatomical) does not influence the prognosis[1].

The timing of surgery

In a patient with liver metastases that can be resected, we can encounter several different situations: individual or multiple, synchronous or metachronous metastases. The most adequate therapeutical strategy can be decided on the basis of the most important studies on the surgical removal of liver metastases, and on the factors influencing the patient's prognosis after surgery. As mentioned earlier, the most important factor is the resection margin, which must be greater than or equal to 1 cm. Other generally undisputed factors are:

– CEA pre-operatory levels,
– the size of the lesions/total mass volume of tumour[8],
– number of lesions (< or > than 4),
– disease-free survival (DFS) <12 months,
– stage of primitive tumour.

In general, the prognosis worsens as the CEA levels, and the number and the size of lesions increase. It seems to be more negative in the case of synchronous metastases than in the case of metachronous lesions, but this is still the object of debate[9, 10]. An individual synchronous lesion of small size should be removed immediately, but in the case of multiple metastases, or lesions located in the deepest parts of the liver, immediate surgery might not constitute the best approach, for multiple reasons.

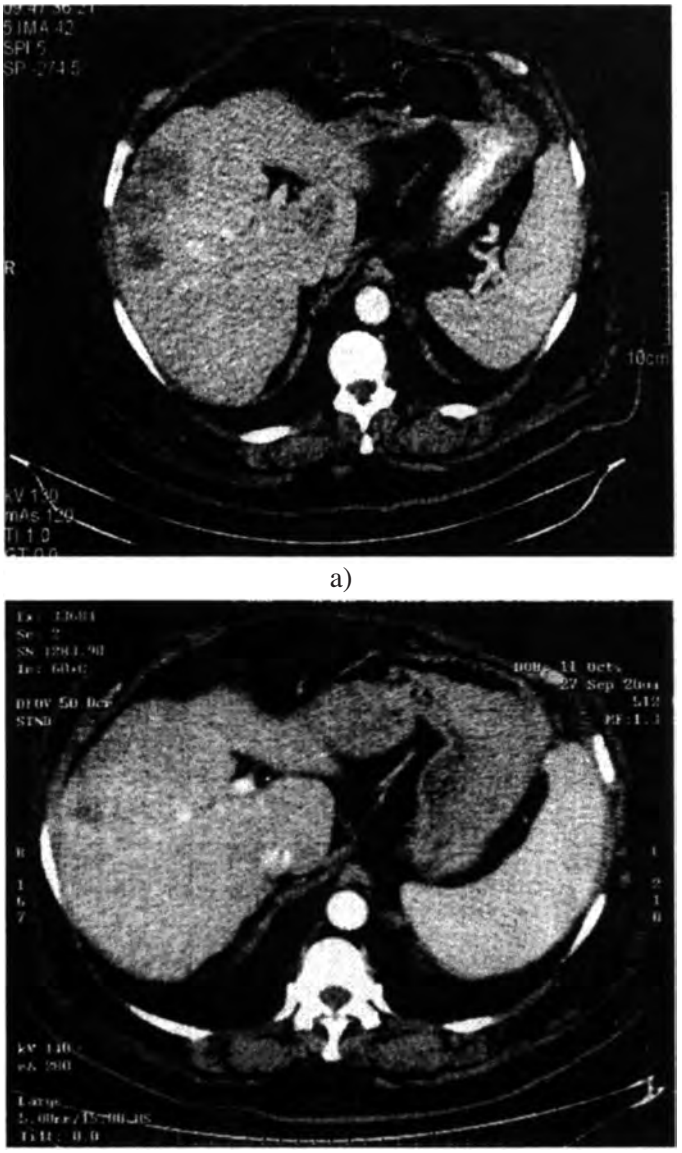
In the case of resectable synchronous multiple lesions, delay of hepatic resection may be justified by two kinds of reasons: surgery should not be performed immediately, first of all for reasons of a technical nature: as a matter of fact, the incision required to remove a primitive tumour is different from that which is optimal for the removal of liver metastases. In addition, the haemodynamic changes that may occur as a result of vascular clamping can lead to complications at the level of digestive sutures[1].

Secondly, and this is true also in the case of multiple lesions, delaying surgery can be useful in order to observe

the natural behaviour of the disease: it would be pointless to let a patient undergo major surgery when the disease is in any case destined to explode and become uncontrollable because of particular biological characteristics. Further, systemic chemotherapy performed at this stage can give us an idea of the chemosensibility of the disease and, at the same time, play a protective function at the systemic level. The disadvantage of a similar approach could be that a progression could occur during the chemotherapy, such that lesions that were initially operable would no longer be so. Wein *et al*[11] published a study on 20 primary resectable patients who had neoadjuvant chemotherapy based on a 5-fluorouracil/folinic acid (5-FU/FA) + oxaliplatin (OHP) schedule. The study showed a response rate (RR) of 100%, with a partial response (PR) of 90% and a complete response (CR) of 10%, with potentially curative surgery in 80% of the patients. DFS at 2 years was 52% and the survival rate after the same period of time was 80%. These results, although obtained on small numbers, give value to the strategy of delaying surgery in the case of multiple, initially-operable metastases and emphasize the rôle of neoadjuvant chemotherapy including new agents (OHP and irinotecan-CPT-11), in such patients.

The inoperable patient

Until now we have considered the minority of patients with liver metastases, since only 10-20% of all patients are judged to be operable immediately after diagnosis. In the remaining 80% of cases, the only available tool, at least initially, is chemotherapy, which, thanks to a combination of 5-FU, OHP, CPT-11, and new agents, leads to a median survival period of 20-22 months[12, 13]. By itself, chemotherapy increases survival rates and the quality of life, but it is not curative. By introducing OHP and CPT-11 coupled with 5-FU, systemic chemotherapy has drastically increased its efficacy in terms of overall survival (OS), time to progression (TTP) and RR. The high levels of objective responses, which have been observed as a result of these regimes, have made it possible to use them with a neoadjuvant aim; they can, in fact, reduce the size of liver metastases and render surgery a viable option for lesions that were initially labelled inoperable (fig. 1). Patients who are diagnosed with a life span of no longer than 19-22 months become potentially operable and are thus given a chance for long-term survival. Bismuth *et al*[14] were the first to complete a retrospective study evaluating the impact of neoadjuvant chemotherapy. The study considered 330 patients who were initially inoperable and therefore treated with OHP-based chronomodulated chemotherapy. Of all the patients, 56 (16%) were



a)

b)

Fig. 1. Metastases of colorectal cancer in the liver before (a) and after (b) chemotherapy with 5-FU-FA and OHP

radically operated with a median survival rate at 5 years of 40%. Thus, it emerged that initially inoperable patients, who undergo surgery after a neoadjuvant chemotherapy, have a survival rate comparable to that of those patients operated immediately. For the first time, then, we see how the prognosis of a patient affected by metastatic CRC has been substantially modified by chemotherapy, although still in association with surgery.

Later studies showed that the percentage of patients who were radically operated after chemotherapy varied between 11% and 38%.

Recently a phase II prospective study by Wein *et al*[15] showed that out of 53 patients treated with a weekly 5-FU/FA-based continuous infusion schedule, 11% were R0 resected. Giacchetti *et al*[16] noted that, out of 151 cas-

es, 38% were operated radically after an OHP/5-FU/FA-based schedule. In this instance as well, the survival rate and the DFS (at 2 years) of these patients were comparable to those of patients who had undergone surgery immediately.

Using a FOLFIRI schedule, Pozzo *et al*[17] completed a study on 40 initially inoperable patients, reporting an RR of 47% (= 19 patients) with 2 CR and 11 stable diseases (SD). Thirteen patients (32.5%) underwent radical surgery after chemotherapy. The effects of this treatment on the survival rate still need to be determined.

Using a FOLFOXIRI schedule, Falcone *et al*[18] managed to radically operate 19 patients out of 74 (26%). The median survival period of all patients was 27 months, compared to 39.6 months for those operated.

Equally positive are responses and resectability rates after combinations of systemic chemotherapy and intra-arterial infused chemotherapy.

A phase I study using a combination of hepatic intra-arterial infusion (HAI) fluorodeoxyuridine (FUDR)+ CPT-11 iv reported levels of response of 74%[19].

Another recent study by Leonard *et al*[20], presented at the 2004 ASCO conference, evaluated the efficacy, in terms of RR and resection rate, of a second line combination of FUDR via HAI+CPT-11/OHP iv or 5-FU/FA/OHP iv in patients whose first line treatment contained CPT-11 or OHP. Out of a total of 44 patients they found an RR of 82% with a resection rate of 20% (= 9 patients) (potentially 36% = 16 patients). The results highlighted in the study were particularly positive because, after the failure of first line systemic chemotherapy with CPT-11 or OHP, the RR of a second line systemic therapy is usually rather scarce (whether CPT-11 or OHP is used), with variations ranging from 4% to 22% according to different studies[12, 21-29], and rescue surgery becomes impossible. The impact of new targeted therapies in a neoadjuvant setting still has to be evaluated.

It is emerging clearly that the introduction of new agents and progressively more effective treatment schedules allow a new type of approach to the unresectable patient, for whom chemotherapy has no longer to be considered only as a palliative treatment, but as a fundamental step in a combined medical and surgical strategy with a curative aim.

Unfortunately only 11-38% of patients with initially judged unresectable lesions are suitable for surgery after a neoadjuvant first line therapy. If at this point surgery is still impossible (in about 60-70% of all patients undergoing neoadjuvant therapy), the main goal is to delay the symptomatic phase of the disease and to prolong survival. This group of patients, who are unresectable, for comorbidities, intrahepatic or extrahepatic spread of the disease, may only be candidates for chemotherapy or other locoregional therapies, such as radiofrequency (RF) ablation or cryosurgery (CS). There is no place for debulking surgery, since the survival of patients who do not undergo radical resection is the same as that of those who are unresected[30]. RF and CS can be also complementary to surgical treatment, when surgery alone cannot obtain surgical radicality. Nowadays RF is used more than CS for practical reasons: although both methodologies are equally effective in terms of local recurrence rates, RF can be performed by a percutaneous access because of the smaller dimensions of the electrodes compared with the probes used for CS, which is mainly performed by laparotomic access.

The size of treated lesions is an important prognostic factor for the outcome of these patients: lesions smaller than 3-4 cm are related to a better outcome, because this kind of lesion can be successfully treated with single needle insertions, whereas metastases larger than 5-6 cm need multiple needle insertions, with an increase in local relapse.

Few studies directly compare the efficacy of CS and RF, and these are difficult to interpret. It seems that for lesions up to 3 cm in diameter, local recurrence rates are low for both techniques, but for lesions larger than 3 cm local recurrence rates start to increase significantly for RF to over 33%. For CS the increase in local recurrences starts to rise from a diameter of 5-6 cm. It is important to observe that, while RF is equally effective if performed by percutaneous or laparotomic access, for CS promising results are only described for the open approach.

When both techniques are performed by a percutaneous access for lesions < 5 cm, local recurrence rates are 53% for CS versus 18% for RF. Data on DFS and OS after RF ablation are equally conflicting and difficult to interpret: many differences exist between the studies, in regard to the size of lesions and the way RF is applied (percutaneous, laparoscopic or laparotomic); moreover in different studies RF is performed alone, in combination with surgery, or completed by chemotherapy (via HAI or systemic)[31-33].

The main still unanswered question regards the radicality of these techniques, because randomized studies directly comparing surgery with RF or CS are lacking, and the impact on overall survival is not clearly defined. Two-year survival after RF varies from 50% to 75%, but once again with the limit that the studies are retrospective and difficult to compare. One year DFS varies from 25% to 50%[31-35]. It is important to distinguish true local relapses (which are low) from new liver metastases related to progression and multifocality of the disease in the liver parenchyma. It could be suitable to conduct systemic

chemotherapy, to complete RF treatment and to reduce the recurrence rate related to the spread of the disease.

Recently two studies directly compare surgery with RF. The first one is a retrospective study of 418 patients: 358 patients had surgery, RF alone or surgery plus RF (in these patients it was impossible to perform a R0 resection); 70 patients were treated with systemic chemotherapy +/- HAI after explorative surgery. Four year survival was 65% for surgery only, 36% for surgery plus RF, 22% for RF alone. The overall recurrence rate was 52% for surgery alone, 64% for surgery combined with RF, 84% for RF alone. The liver recurrence rate was 11% for surgery *vs* 44% for RF alone. The true local relapse rate was 2% with surgery alone, 5% with surgery plus RF, 9% with RF.

Surgery was related to the best outcome. RF had a higher recurrence rate and a worse 4 year survival[36]. The data therefore suggest that surgery is better. A further result of this study is that RF provides survival only slightly superior to nonsurgical treatment. However in this study the comparison was made between operable and not completely operable patients, and patients candidate to RF treatment, for whom surgery was not feasible: the latter were those with a worse prognosis, whereas the former – those treated with surgery – had a better prognosis. A well-designed study should directly compare surgery and RF in primary resectable patients with liver metastases. A non randomized study from Oshowo *et al*[37] considered 45 consecutive patients with single liver metastases: 20 of them received surgery and 25 were treated with RF. For the 25 patients treated with RF the resection was not feasible for technical reasons (ill-located lesions) (9 patients), comorbidities (9 patients), extrahepatic lesions (7 patients). The median OS after surgery was 41 months (55.4% alive at 3 years) *vs* 37 months (52.5% alive at 3 years) after RF. This study was too small to draw any conclusions and a prospective, randomized trial comparing surgery and RF in operable patients is lacking, but such a study would, in all likelihood, be extremely difficult to conduct.

Adjuvant therapy for resected patients

Surgery remains the gold standard of care, but with two fundamental limits. First, only a minority of all patients with liver metastases can be resected: in this case the resection rate can be sensibly increased by a neoadjuvant chemotherapy. The second limit is the high recurrence rate.

Without going into detail as to whether patients have been pre-treated or not, suffice it to say that most patients in the available studies are not pre-treated. The recurrence rate after surgery in most studies is about 75% and, in half of these cases, the liver is affected. Sixty-six percent of all relapses are observed within the first 12 months after surgery. The questions to be faced are two: how to improve the results of surgical treatment, and how to reduce the rate of recurrence.

Prospective randomized trials on the impact of adjuvant chemotherapy after metastasectomy have investigated only the rôle of HAI, or combinations of HAI and systemic chemotherapy.

Only retrospective studies have investigated the rôle of adjuvant systemic chemotherapy alone.

Some years ago Lorentz *et al*[38] compared surgery alone with surgery plus HAI (with a 5-FU/FA-based schedule): they did not find any survival advantage for the treated arm, reporting also a considerable toxicity.

One year later, a study from the Memorial Sloan Kettering Cancer Center compared HAI FUDR+ systemic 5-FU/FA with systemic 5-FU/FA alone, showing a decrease in the hepatic recurrence rate and an improved OS only at 2 years for the combined treatment[39]. The control arm of this study seems to be inadequate, because a direct comparison with the observation alone is lacking and new standard regimens containing 5-FU in combination with OHP and CPT-11 are more effective than 5-FU/FA alone in the advanced phase of the disease and also in the adjuvant setting after resection of the primary tumour[40].

Three years ago Kemeny *et al*[41] published data from a study carried out on 75 patients, comparing the outcome of patients treated with HAI + systemic 5-FU c.i. with those kept under observation: they showed a reduced risk of recurrence, but once again no advantage on survival for the treated arm. No recent data concerning these studies are available.

From these studies we can deduce that HAI alone does not provide any survival advantage compared with observation alone. HAI associated with systemic chemotherapy (5-FU/FA schedules) showed only a decrease in the recurrence rate and consistent toxicity, with no advantage on survival. Future trials will evaluate the efficacy of combinations of HAI with systemic 5-FU, OHP and/or CPT-11, which are very promising and effective as first line treatment. The main limitations of HAI are: first, the risk of extrahepatic progression, which is increased, because only the liver receives a sufficient concentration of the drug; that is why recent trials combine HAI with a systemic treatment. The second main limit is the risk of severe side effects; first of all hepatic toxicity, with hepatitis and biliary sclerosis. These side effects were observed exclusively with FUDR and were dependent of dose and duration of administration. The co-administra-

tion of dexamethasone can reduce the incidence of severe biliary sclerosis.

Until now only few retrospective studies investigated the rôle of an adjuvant systemic chemotherapy after resection of liver metastases, some of them showing an interesting trend of survival advantage and decreased recurrence rate for patients receiving chemotherapy[42]. An adjuvant multicentre trial is now in progress in Europe but recruitment difficulties are a big obstacle for this study.

The Saint Orsola Hospital experience

In cooperation with the surgeons of our hospital, we carried out a retrospective study on 84 consecutive patients (45 M age 45-73 years) with liver metastases at first recurrence after R0 resection[43]. Twenty-seven patients received an adjuvant 5-FU/FA +/- OHP or CPT-11 based chemotherapy; 57 did not received any medical treatment. The characteristics of patients, the number of metastatic lesions in the liver, the size of the lesions were compared in the two groups (Table 1). All patients were at first metastatic recurrence and underwent a R0 resection. The DFS at 40 months was higher in treated than in untreated patients, with a median value of 13.3 *vs* 9.3 months, but with no significative difference (p = 0.081), probably because of the small number of patients included (fig. 2).

These results suggest that systemic adjuvant chemotherapy after resection of metastases of colorectal cancer could have a rôle in improving the prognosis of these patients, and could be suitable for patients at high risk of recurrence. A larger multicentre retrospective analysis is in progress, but prospective trials seem to be more suitable to clarify this controversial point. Finally we know that up to 70% of all patients undergoing resection will develop recurrence, one third of which will be confined to the liver[44]. In these patients it seems to be a good strategy to perform a second and even a third hepatectomy whenever possible, since most series report a survival benefit for second and third hepatectomy comparable to that of first hepatectomy, with the same morbidity and mortality rates[45, 46].

Table 1 - Comparison of two groups in a retrospective analysis of adjuvant chemotherapy after surgical resection of liver metastases from colorectal cancer

	Treated	Not treated	p value
Number	27	57	NS
Mean age	57.9	59.6	NS
Mean time to re-evaluation (months)	4.7 ± 0.2	4.5 ± 0.3	NS
Number of metastases (mean)	2.1	1.9	NS
Single/multiple metastases	13/14	19/38	NS
Synchrone/metachrone metastases	15/12	19/38	0.008
DFS >/< 12 months	9/18	26/31	NS
Adjuvant chemotherapy	7/5	21/17	NS

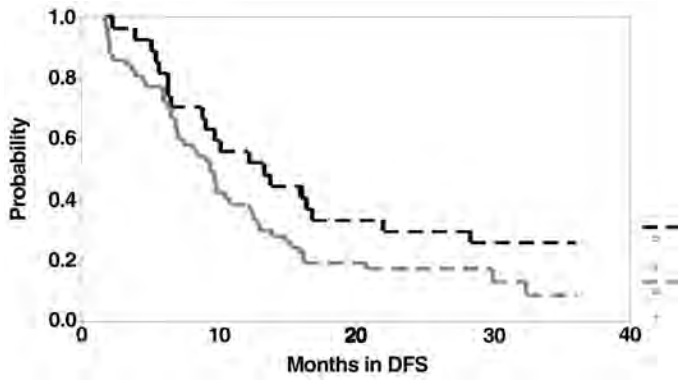


Fig. 2. Disease-free survival of 84 patients with liver metastases at first recurrence who were R0, resected in our centre. Twenty-seven patients had an adjuvant post-operative chemotherapy (black line), 57 did not (grey line), with a median DFS of 13.3 months *vs* 9.3 months respectively for treated and untreated patients (p = 0.081).

Conclusions

Some doubts are still persisting about the better choice in the treatment of liver metastases from colorectal cancer. When surgery is not indicated, local chemotherapy is a valid therapeutic challenge. However, as previously considered, this strategy requires experience and awareness of the associated side effects. Moreover the procedure is very expensive and a substantial gain of survival in comparison with intravenous therapies is still to be proved. On the contrary, systemic treatment with new regimens containing 5-FU and OHP or CPT-11 have demonstrated to lead to an improvement in the survival of patients with advanced disease.

This is the present state of therapeutic possibilities. But the scenario is rapidly changing. New drugs are being proposed for local intravenuos or HAI treatments, new local strategies such as surgical approaches or radiofrequency ablation alone or together are being tested in phase II trials, new agents are demonstrating efficacy in the treatment of advanced disease. There is currently a debate in the scientific community, about these new biological therapies. The antibody anti-EGFr (epidermal growth factor receptor) and the antibody anti-VEGFr (vascular endothelial growth factor receptor) are ap-

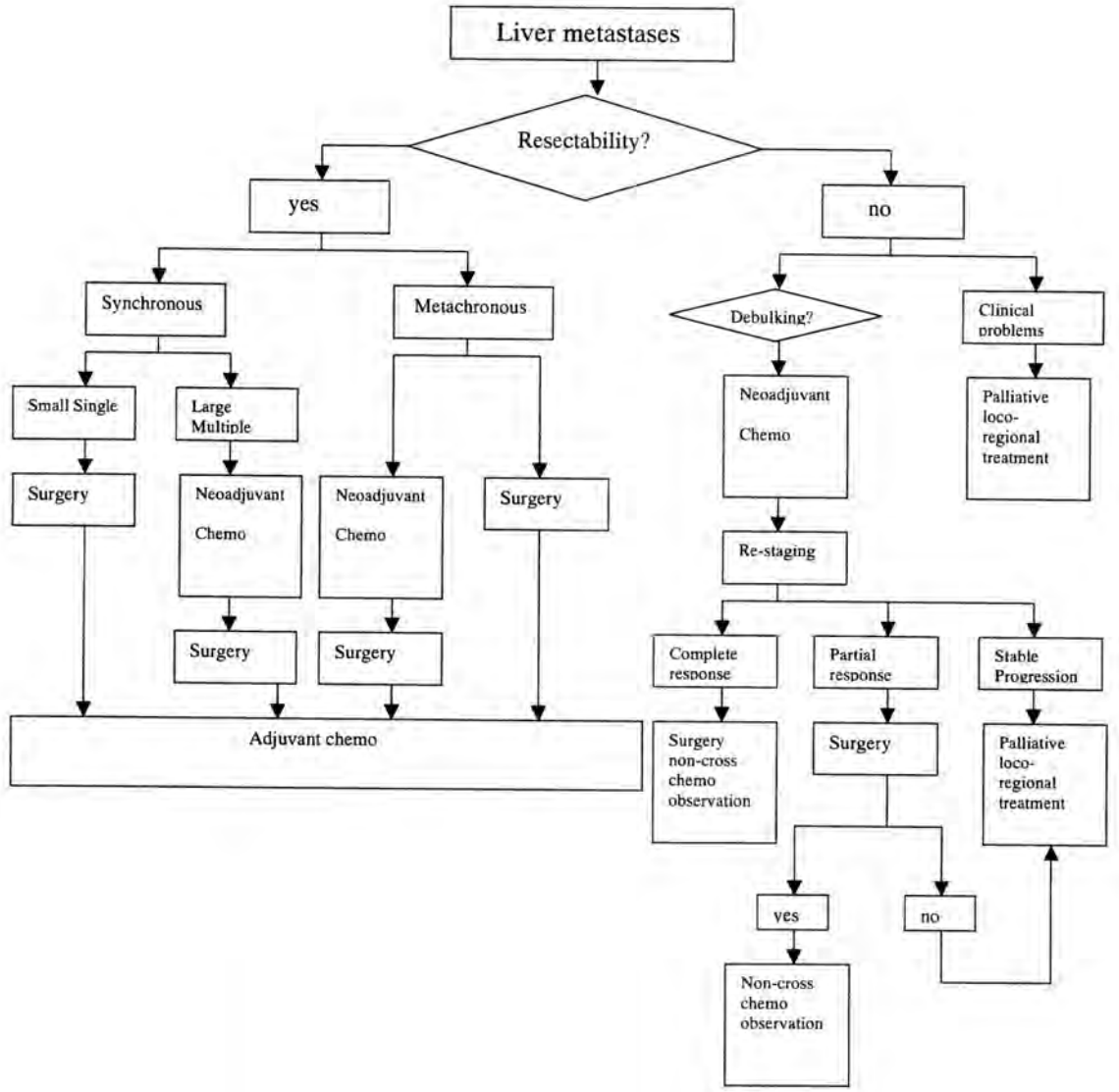


Fig. 3. A decisional flow-chart for the treatment of liver metastases from colorectal cancer

proved for the clinical use after the results of phase II and III trials, however they are very expensive and, most importantly, definitive criteria of patients' selection for therapy have not yet been established.

In conclusion, new perspectives in the treatment of liver metastases from colorectal cancer have been opening. The new options are so many to lead to the risk of having more choices than patients for acceptable clinical trials. So, at the moment, a "stop for thinking" appears to be appropriate to avoid confusion in the clinical practice. Waiting for the results of the future trials, we should pragmatically follow established criteria of treatment. This can allow to design acceptable flow charts (fig. 3). The availability and the experience of the local surgical team are of fundamental importance.

Three years ago we published a review paper[47]. The question was "What is the best approach for the treatment of liver metastases from colorectal cancer?". In these years some progress has been made but the question has not yet a definitive answer.

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Eur. J. Oncol., vol. 10, n. 1, pp. 55-62, 2005

The epidemiology of neuroendocrine tumours. The dimension of a problem, a problem of dimension

L'epidemiologia dei tumori neuroendocrini. La dimensione di un problema, un problema di dimensione

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Summary

Neuroendocrine tumours (NETs) are rare neoplasias with a clinical mean incidence of 1 case/100,000/year. On the basis of the numerous data gathered by our General Surgery Unit over the last 14 years, it is clear that the clinical and epidemiologic dimension of the problem related to NETs cannot be immediately assessed, on the one hand because there is a prevalence of asymptomatic tumours and, on the other, because, data on the clinical incidence of the disease are, in some cases, in contrast with those of *post-mortem* prevalence. A particularly sensitive factor derives from the clinicians' degree of knowledge about the issue and from the fact that neuroendocrine tumours, being rare, may arouse little interest in the scientific community, thus leading to an underestimation of the problem. Selective screening for some typical aspects of the symptomatic tumours may help to give a more realistic epidemiological picture. For this reason, it will be necessary in the future to exploit all possible resources, in order to obtain data which are more and more realistic and less and less approximate. Eur. J. Oncol., 10 (1), 55-62, 2005

Key words: **neuroendocrine tumours, carcinoid, epidemiology, screening, diarrhoea**

Riassunto

I tumori neuroendocrini (NETs) sono neoplasie rare con una incidenza clinica media pari a 1 caso/100.000/anno. Da numerosi dati raccolti dalla nostra Unità Operativa di Chirurgia Generale nel corso degli ultimi 14 anni, si può osservare che la dimensione clinica ed epidemiologica del problema NETs non si presta ad una valutazione immediata, da un lato per la preponderanza di tumori asintomatici, dall'altro perché i dati di incidenza clinica della malattia contrastano in alcuni casi con quelli di prevalenza autoptica. Un fattore particolarmente sensibile deriva dal grado di conoscenza del problema da parte del clinico e dal fatto che i tumori neuroendocrini, in quanto rari, possono destare scarso interesse da parte della comunità scientifica, col risultato di una sottostima del problema. Lo screening selettivo su alcuni aspetti che caratterizzano i tumori sintomatici potrebbe aiutare a dare una immagine epidemiologica più vicina alla realtà. Per tale motivo sarà necessario in futuro utilizzare tutte le risorse in nostro possesso allo scopo di ottenere dati sempre più realistici e sempre meno approssimativi. Eur. J. Oncol., 10 (1), 55-62, 2005

Parole chiave: **tumori neuroendocrini, carcinoide, epidemiologia, screening, diarrea**

Received/Pervenuto 3.11.2004 - Accepted/Accettato 16.12.2004
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Introduction

Neuroendocrine tumours (NETs) are hormonal neoplasias with a low incidence (approximately 1 case/100,000/year), commonly known as rare disorders.

In most cases, NETs are well-differentiated tumours associated with a low grade of malignancy and long survival, and they are often characterized by an unpredictable clinical course, due to the presence of disabling symptoms which are difficult to control (e.g. refractory chronic diarrhoea); relapses sometimes occur after long time.

On the contrary, in 20-30% of cases, NETs are advanced malignancies with metastases, primarily to the liver. In other cases, they are poorly differentiated tumours with an unfavourable short-term prognosis, being able to metastasize even to the skin.

NETs may be a sporadic condition or a familial disease diagnosed in patients belonging to families who are known to have hormonal disorders.

From 1990 to date, our General Surgery Unit has studied 151 cases of neuroendocrine gastroenteropancreatic tumour, 17 cases of bronchial carcinoid tumour, 10 cases of Merkel cell carcinoma, 6 cases of adrenal pheochromocytoma, 3 cases of medullary thyroid carcinoma, as well as NETs in other regions (soft tissues, paranasal sinuses, breast, paraganglions).

These findings have induced us to consider the epidemiologic aspects of NETs, since the large number of our case studies lets us suppose that epidemiologic relevance of these tumours has changed over the last ten years. One reason may be identified in the fact that our Unit has become a national benchmark for this disease over the years; but there have also been important technological developments, recorded over the last 15 years, both in nuclear medicine and radiological imaging, and in laboratory techniques, all of which have facilitated the diagnosis of these tumours. Another reason may be associated with the multifactorial origin (genetic and environmental) which may have caused an increase in the incidence of these tumours.

Based on these premises, we have thought it might be necessary to verify historical, epidemiologic, diagnostic and cultural criteria which may contribute to a correct quantification of NETs, in order to identify the basic tools which may demonstrate that this disease is less rare than expected.

Diffuse neuroendocrine system

More than 60 years ago, Feyrter[1] had postulated the presence of a diffuse neuroendocrine system, which might be affected by tumours with identical morphologic and secretory characteristics - the so-called "*helle zelle*" (cells endowed with a light cytoplasm) distributed throughout the human body - by reworking hypotheses which had been already suggested by Heidenhain in 1870 and then by Gosset and Masson in 1914[2] and Hamperl in 1932.

In the sixties, Pearse[3] also made his contribution to the classification of NETs, by identifying a system known with the acronym APUD (Amine Precursor Uptake and Decarboxylation), including cells with similar ultrastructural, cytochemical and metabolic characteristics, as well as with the same embryologic origin from the neural crest.

Refined chimerism tests, performed by Fontaine and Le Douarin[4], Le Dourain[5] and Andrews in the seventies, showed the presence of neuroendocrine cells having also an embryologic endodermal origin, thus confuting Pearse's concept of the APUD cell and extending the classification for this group of tumours.

More recently, tissue staining procedures, molecular biology techniques and the research on some specific cellular markers have enabled us to identify some important criteria for defining a neuroendocrine cell[6]:

- neuroendocrine cells produce a neurotransmitter, a neuromodulator or a neurohormone;
- these chemical agents, which are inside cytoplasmic vesicles, are released through exocytosis in response to external stimuli;
- neuroendocrine cells differ from nerve cells for the absence of axons and specialized nerve endings;
- many neuroendocrine cells express the same type of protein marker.

Thanks to these original ideas, the concept of the neuroendocrine cell has developed and changed over almost one Century, so that nowadays prostatic[7-10], ovarian[11, 12], testis[13], renal[14, 15], breast[16], thymic[17-19] and laryngeal[20-23] endocrine tumours may be discussed, without arousing great amazement. Moreover, the old barrier between what is endocrine and what is not may be removed, supporting a novel concept of the endocrine cell. This original idea poses new problems relating to its classification and epidemiology, and leads on to consider the dimensions of the problem related to NETs which, at this point, may be unlimited and certainly different from those conceived up to now.

Somatostatin and its analogues

In vivo research on receptors for somatostatin and its analogues has highlighted new useful elements to define the characteristics of neuroendocrine cells.

At the beginning of the nineties, Lamberts *et al* [24] demonstrated *in vivo* the presence of specific receptors

for analogues of somatostatin even on cells which were not closely related to the neuroendocrine system, using a labelled analogue (^{111}In pentetreotide)[24]. Lamberts made a personal reassessment of Feyrter's concept of a diffuse neuroendocrine system, in order to provide clinicians with a novel diagnostic and therapeutic instrument, but he also posed a new problem relating to the classification: do neuroendocrine cells share the same hormonal receptors? Or, is the presence of these receptors enough to define NETs in any case?

Sensitivity to ^{111}In pentetreotide is very high (75%) in breast carcinoma, whereas it is extremely high (85%) in infiltrating ductal carcinoma[25]. Small cell lung carcinoma has several characteristics in common with NETs, such as the tissue expression for Neuron Specific Enolase (NSE), chromogranin A and synaptophysin[26], as well as sensitivity and specificity to ^{111}In pentetreotide corresponding to 100% of cases[27]. The same can be said both for meningioma, which in some works in the literature[24, 28, 29], has shown high sensitivity to ^{111}In pentetreotide (100%), and for some lymphoproliferative disorders, whose sensitivity to ^{111}In pentetreotide ranges from 13% to 100% of cases[30-36].

The problem is becoming more complicated.

Epidemiology

By turning on the computer and connecting to one of the most famous scientific search engines (such as PubMed), it is possible to find a variety of items relating to NETs: approximately 50,000 just for therapy, more than 20,000 for surgery, and 10,000 for chemotherapy. It is the same both for scientific protocols created over the last 15 years, and for the large number of international meetings on this disease.

These figures indicate how the problem relating to NETs is being discussed in the literature and how the scientific community has realized the need for a better understanding of this issue.

These tumours are undoubtedly rare, based on published data about their incidence. In fact, the mean incidence of NETs is around 1 case/100,000/year[37-55] (Table 1).

However, a great discrepancy explaining clinicians' difficulty in diagnosing these tumours is observed, when comparing data of clinical incidence with those of *post-mortem* prevalence, estimated at 8.4 cases/100,000/year[56] and at 1,500 cases/100,000/year[57] in relation to carcinoids and to endocrine pancreatic tumours, respectively, although these results are not statistically comparable.

This is certainly due to the fact these tumours are asymptomatic (non functioning) in 80% of cases. And, even in the case of a symptom or a syndrome being distinctive of this disease (chronic diarrhoea is a typical example), clinicians are inclined to believe that the low frequency of these tumours may represent a good reason to exclude them *a priori* from diagnostic suppositions.

Table 1 - Clinical incidence and frequency of neuroendocrine tumours

Tumour	Incidence or frequency[a]
Midgut carcinoid	0.8-2.1/100,000/year
Gastric carcinoid	< 1% overall gastric tumours
Large bowel carcinoid	< 1% overall bowel tumours
Rectal carcinoid	1-2% overall rectal tumours
Pancreatic endocrine tumours	0.4/100,000/year
insulinoma	1/1,000,000/year
glucagonoma	0.2/1,000,000/year
gastrinoma	0.05-2/1,000,000/year
VIPoma	0.05-0.2/1,000,000/year
Typical bronchial carcinoid	2% overall lung tumours
Phaeochromocytoma	0.8/100,000/year
Medullary thyroid carcinoma	< 10% overall thyroid tumours
Merkel cell carcinoma	0.2/100,000/year

[a] Data on these tumours are very scarce. The Table provides the data which are available

In Italy, an important project, the GEP Project (data base on gastroenteropancreatic endocrine tumours) was carried out to verify the number of cases of digestive NETs in this country: it involved 45 centres located in 32 towns, it collected 470 cases from 1995 to 1998, including a retrospective analysis of appropriately documented cases since 1960[58, 59], and it was concluded in 1998 (fig. 1).

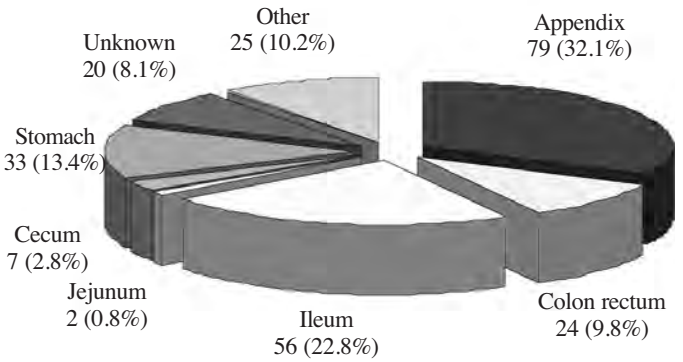
NETs have been proven to exist: it is necessary to learn how to detect them.

Laboratory

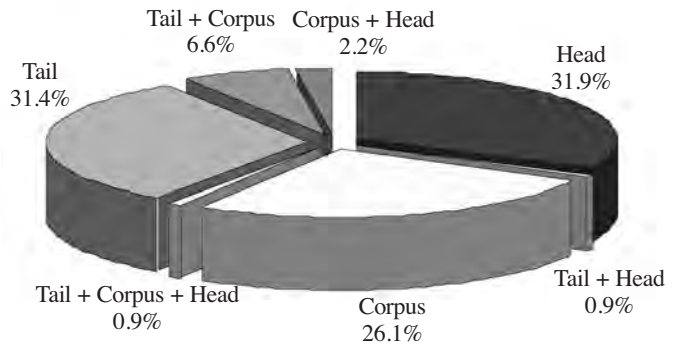
It is a well-known fact that the laboratory diagnosis of NETs is linked to the measurement of some plasma peptides and other markers, including NSE and chromogranin A, an acid protein that belongs to the family of granins.

Several studies suggest that the measurement of chromogranin A is very useful in patients with NETs – such as phaeochromocytoma, neuroblastoma, midgut carcinoid tumour and small cell lung tumour – with an increase in plasma values in 50-100% of cases.

It is a well known fact that the measurement of plasma chromogranin A in patients with NETs provides a consid-



Gastrointestinal neuroendocrine tumours



Pancreatic endocrine tumours

Fig. 1. GEP Project: frequency of digestive neuroendocrine tumours. From De Angelis *et al*., 2002[58, 59], modified

erable diagnostic accuracy, with a sensitivity of 70-90% and specificity of 70-80%[60-71].

These findings have aroused interest in NETs and have contributed to further extend the epidemiologic dimension related to biology, evidencing high chromogranin A plasma levels even in tumours which are not usually considered as neuroendocrine disorders, such as prostatic tumour[72, 73].

Moreover, tissue immunohistochemical tests now allow a modern approach to the pathological diagnosis of NET, including the use of several parameters of evaluation, such as angioinvasivity, mitotic index, cell proliferation index (Ki67), and the expression of specific proteins, such as chromogranin A, NSE, synaptophysin and vimentin[74-82], which have enabled us to exceed the diagnostic limit imposed by the grading, increasing the number of new diagnoses and consequently modifying the epidemiologic dimension of the problem.

This issue becomes broader and more complicated, if considering the problem in relation to molecular biology, highlighting the hypothesis of genetic involvement not only for hereditary forms[83]. This fact has new implications for the classification. It will soon be necessary to revise the latest classifications for NETs, using new parameters of identification, and to recognize the ploidy status as a prognostic indicator[84].

Imaging

The technological developments in nuclear medicine and radiological imaging have allowed a better understanding of NETs, identifying an ever-increasing number of lesions and the subsequent escalation in their diagnosis[85-90].

The diagnostic approach with ^{111}In pentetreotide, having sometimes a higher sensitivity than the radiological one, has enabled us to change the clinical and therapeutic approach, so avoiding the surgical approach when unnecessary in a large proportion of cases (21-47% of cases) [91-94].

The recent development of diagnostic procedures, such as Positron Emission Tomography (PET)[95], along with X-ray imaging fusion, has allowed further improvement in the therapeutic approach to NETs in up to 30% of cases, extending the role of imaging in the diagnostics of these tumours[96-99].

A cultural dimension of the problem

In addition to explicit epidemiologic and classificatory aspects, there is also a cultural dimension of the problem related to NETs, which should not be underestimated and is related to the clinicians' degree of knowledge about this issue.

In fact, NETs belong to the group of rare neoplasias and, for this reason, they may be disregarded by clinicians, who are more involved in organisational and operating aspects related to more common neoplastic disorders.

Patients are often addressed to centres, where the knowledge of NETs is partial, and technological resources used for the diagnosis and opportunities to find a correct treatment are very limited. The presence of centres with a different degrees of experience has induced a great and constant drift of patients in search of certainty, both in terms of diagnosis and therapy. Moreover, in many cases, it is not easy for patients to obtain some certainty, compelling them to support an additional burden, not only in terms of expense[100].

This drift of patients represents another issue: the same subject may be included in several databases, thus creating subsequent problems related to the epidemiologic interpretation of data as well as an incorrect dimension of the problem.

Lastly, data dispersion prevents the collection of adequate samples, which are consequently poorly statistically significant.

New terms have been already included in the medical vocabulary, such as Diagnosis Related Groups (DRG), an instrument whose improper use may reduce the interest in NETs, since these types of tumour do not produce the benefits associated with more common oncologic diseases, thus underestimating the problem.

Screening for epidemiology

Screening for NETs may appear to make little sense. In fact, the high proportion of non-functioning cases prevents these tumours from being clinically recognized and, as previously stressed, despite the evidence of common symptoms associated with this disorder, such as chronic diarrhoea and relapsing peptic disease, there is no incentive to proceed with targeted investigations in most cases.

Taking for granted the relevance of screening for familial diseases, which has consolidated its own rationale of use[83] for long time, the question is whether to recognize screening as being useful for those symptoms (namely, gastritis, relapsing peptic disease and chronic diarrhoea) which may mask a hormonal neoplasm, as well as whether this fact may alter the epidemiologic dimension of NETs.

Gastrinoma is one of the most common and most investigated hormonal disorders[43, 101]. It is a well-known fact that peptic disease is usually observed in 93% of cases with Zollinger-Ellison syndrome[102]. The indiscriminate use of antisecretory agents (H_2 antagonists, protonic pump inhibitors) has led to the masking of early clinical manifestations[103], thus reducing the presence of peptic disease to just 18-25% of cases in recent studies[104] and extending, inevitably, the mean time between the onset of symptoms and the diagnosis of the disease by up to 6 years[105]. In our opinion, even if gastrinoma is only observed in 0.1-1% of all patients with peptic ulcer disease[106], the determination test of plasma gastrin level in all dyspeptic disorders may be extremely useful both for the early determination of hormone-related forms and for the correct assessment of the epidemiology of gastrinoma.

There are many forms of disease associated with chronic diarrhoea, as well as many NETs correlated with diarrhoeal events. In a small study, we enrolled diarrhoeic patients in order to verify how many of them really suffered from NETs. Patients were experiencing diarrhoeal events from at least 3-4 weeks (frequency: not less than 6 loose stools a day), and they were refractory to common antidiarrhoeal drugs. These patients underwent the determination test for plasma gastrin (a common marker of many neuroendocrine diseases), NSE and 5-HIAA urine level[107].

The findings from this study were not high (true-positive tests <3%), but confirm that early diagnosis of some functioning NETs allows resources to be saved, a better quality of life for patients to be ensured and, in terms of epidemiology, a more realistic dimension for the problem of NETs correlated with chronic diarrhoea to be defined.

Conclusions

The dimension of the issue relating to NETs has many aspects. The quantification of the problem cannot be immediately assessed, because there is a prevalence of asymptomatic tumours and data about the disease-related clinical incidence are in contrast with those of *post-mortem* prevalence in some cases. A particularly sensitive factor derives from the clinicians' degree of knowledge about the issue and from the fact that NETs, being rare, may arouse little interest in the scientific community, thus underestimating the problem.

Selective screening for some typical aspects of the symptomatic tumours may help to give a more realistic epidemiological picture.

NETs represent a current condition. It is therefore necessary to exploit all possible resources in order to obtain data which are more and more realistic, and less and less approximate.

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Eur. J. Oncol., vol. 10, n. 1, pp. 63-67, 2005

Ductal lavage: a new look inside the breast

Lavaggio duttale: un nuovo metodo per valutare la mammella

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Summary

Intraductal breast fluids containing exfoliated mammary epithelial cells can be harvested from the breast by ductal lavage (DL), to screen for disease-associated cytological abnormalities. In the current study the authors investigated the safety and tolerability of DL, and its ability to detect abnormal cells in women at high risk for the development of breast carcinoma. The procedure involves the insertion of a microcatheter, approximately 1.5 cm in depth, into the nipple orifice after local anaesthesia; the lavage of the cannulated ductal system with 1% lidocaine and normal saline solution and the analysis of the collected lavage effluent for the detection of the presence of normal, atypical, or malignant breast ductal cells. Breast fluids were harvested from 75 individual ducts in 67 female patients by DL. Adequate samples for diagnosis were collected from 58 (86.6%) cases. Abnormal cytology was detected in 12 (17.9%) cases: 9 (13.4%) with mild atypia and 3 (4.5%) with marked atypia. Serious procedure-related adverse events were not reported. DL is a safe and minimally invasive procedure that can provide additional information regarding elevated risk for developing breast carcinoma. However, the clinical utility and long-term predictive value of DL require further evaluation. Eur. J. Oncol., 10 (1), 63-67, 2005

***Key words*: ductal lavage, high-risk women, atypia, breast cancer**

Riassunto

I liquidi intraduttali della mammella contenenti cellule epiteliali esfoliate possono essere raccolti mediante lavaggio duttale (LD) per evidenziare anomalie citologiche correlate alla malattia. In questo studio gli autori hanno valutato la sicurezza, la tollerabilità e la capacità di individuare cellule abnormi mediante LD nelle donne ad alto rischio di sviluppare un carcinoma mammario. La metodica prevede l'inserimento di un microcatetere alla profondità di circa 1,5 cm nell'orifizio del capezzolo dopo anestesia locale, il lavaggio con lidocaina all'1% e soluzione fisiologica del sistema duttale incannulato, e l'analisi del liquido di lavaggio raccolto per valutare la presenza di cellule mammarie duttali normali, atipiche o maligne. I liquidi mammari sono stati raccolti mediante LD da 75 singoli dotti in 67 pazienti femmine. In 58 casi (86,6%) sono stati ottenuti campioni adeguati per una diagnosi. Anomalie citologiche sono state osservate in 12 casi (17,9%): 9 (13,4%) con atipia moderata e 3 (4,5%) con atipia marcata. Non sono stati riferiti gravi effetti avversi connessi con la metodica. Il LD è una metodica sicura e scarsamente invasiva, che può offrire informazioni aggiuntive su un aumento del rischio di sviluppare un carcinoma mammario. Tuttavia l'utilità clinica ed il valore predittivo a lungo termine del LD richiedono un'ulteriore valutazione. Eur. J. Oncol., 10 (1), 63-67, 2005

***Parole chiave*: lavaggio duttale, donne ad alto rischio, atipia, carcinoma mammario**

Received/Pervenuto 25.11.2004 - Accepted/Accettato 4.1.2005
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Introduction

The breast is a renewing tissue in which epithelial cells lining the ductal-alveolar mammary tree are exfoliated into the luminal compartments of the gland. Published studies with long follow-up clearly demonstrate that women with atypical ductal epithelial cells have a 3.7 to 5.3 fold increased relative risk of developing breast cancer[1-3].

To increase the amount of fluid obtained and the number of ductal cells harvested with the traditional method of nipple aspirate fluid (NAF), ductal cells have been collected using a modified breast pump[1,4], with catheter insertion for fluid instillation followed by breast massage for fluid recovery[5-7], and by random periareolar fine-needle aspiration[2].

Investigations of NAF have been limited primarily because of the small quantity of fluid obtained. Researchers anticipate that ductal fluid obtained from ductal lavage (DL) will be more informative than traditional NAF because of the larger quantity, the increased cellularity, and the greater probability of obtaining fluid from a given individual[5, 8, 9].

DL is a newly developed and minimally invasive outpatient technique for harvesting fluids and cells from the breast ducts. Potential applications of this procedure include screening, risk assessment and investigation of molecular pathways leading to the development of mammary carcinoma. In a recent multicenter clinical trial, the cytological evaluation of DL specimens which had been collected from asymptomatic, high-risk women, revealed abnormalities in 24% of the specimens[5].

The aim of the present study was to assess the safety and tolerability of DL and its ability to detect abnormal epithelial cells in women at high risk for developing breast carcinoma.

Patients and methods

Our prospective study was concerned with 126 adult, non-pregnant, non-lactating women with benign breast diseases, clinically and mammographically proven.

The patients' ages ranged from 37 to 63 with a mean age of 48.2. Nineteen of the women had had previous breast biopsies. All the patients were at high risk for developing breast carcinoma (5-year Gail risk >1.7%)[10].

There were fourteen reports of periodical spontaneous secretion from papilla; the remaining 112 had no such symptoms. Breasts that had had undergone surgery within 3 cm of the nipple were excluded from the study because of probable disruption of the ductal system. Informed consent was obtained in all cases.

After local anaesthesia applied on the papilla for 30-45 min with EMLA cream (2.5% lidocaine, 2.5% prilocaine, Astra Zeneca, Sweden), the papilla was warned with saline solution for about 5 minutes. The purpose of warming was to relax the sphincters of the nipple. The skin of the papilla was dekeratinizated with Masque Desicrustant (Oriflame Int, Ireland), and then the papilla was gently massaged for 1 minute. Vacuum aspiration was performed with an aspiration pump (NUK Chicco, Italy). Subjects whose breasts did not yield fluid on the first attempt were invited to return for up to 3 repeated attempts before being discontinued from the study.

As a result of the technique described some drops of ductal secretion were collected in capillary tubes in 82 of the cases (65.1%) and cytological examination was performed.

After the nipple aspiration a microcatheter was inserted into the orifice of the secreting duct to a depth of 1-1.5 cm. Two versions of microcatheter were utilized (Vygonule V, G24, d=0.7 mm, Vygon, Germany in 72 cases, and In Duct Breast Microcatheter, Pro Duct Health, USA in 10 cases). In some cases the insertion of the microcatheter was eased by preliminary dilatation of the duct with a dilator (In Duct Breast Ultra Slim Micro Dilatator, Pro Duct Health, USA).

One-three ml of lidocaine 1% was infused intraductally through the microcatheter, followed by 3-5 ml of saline solution. Then the mammary gland was gently massaged from the base to the papilla and the insufflated solution was aspirated. DL was performed once or twice and the aspirated fluid was centrifuged and cytologically examined.

Cytological findings were categorized as insufficient for diagnosis (less than 10 epithelial cells or unacceptable technical quality), benign, atypical (mild or marked) or malignant. All slides were examined by the same pathologist (AT).

DL can be used for individual diagnostics of different ducts and the position of each can be marked on a 64-square nipple grid to allow future cannulation of the same duct.

Results

Fluid-yielding ducts were identified in 65.1% (82 of 126) of all cases. The average number of NAF yielding ducts per breast was 1.2 (1-3). The mean volume of collected fluid was 35 μl (5-95 μl).

Sixty-one of 82 patients produced cell populations containing foam cells; 49 of them contained ductal cells. Thirty-seven (45.1%) of all cases were inadequate for

diagnosis, 39 (47.6%) were benign, 5 (6.1%) were mildly atypical and 1 (1.2%) was markedly atypical.

DL was attempted in 75 breast ducts (67 patients) on a total of 99 fluid-yielding ducts. In the remaining 24 ducts with secretion, despite the use of a microdilatator, perfect illumination, 8x optical magnification and repeated attempts, the cannulation of the duct failed. The mean volume of fluid (1% lidocaine and saline) infused during the DL was 7 ml (5-8 ml), and mean effluent volume was 4.5 ml (4-6 ml).

Lavage samples adequate for diagnosis were collected from 58 (86.6%) women. On average, non-epithelial cells accounted for 50-60% of the total cells in the DL specimens. There were often large histiocytes and foam cells, as well as inflammatory cells. Twenty DL fluids contained epithelial cell clusters in addition to single epithelial cells. Benign epithelial cells were detected in 46 (79.3%) cases and atypical cells were detected in 12 cases (20.8%). Nine of these (15.6%) had cells classified as mild atypia and 3 (5.2%) had cells classified as marked atypia (figs. 1-3). Until now samples with malignant cells have not been observed (Table 1).

After biopsy in 5 of the DL cases with atypia (the three with marked and the two with mild atypia) the histological results were: 3 proliferative papillary lesions and 2 atypical hyperplasias.

During the study no serious procedure-related adverse events were reported. At the time of lavage 14 (20.9%) of the patients suffered from breast pain and 21 (31.3%) reported minor discomfort (heaviness, strain in the breast). Most adverse events were of limited duration.

Table 1 - Overall cytological diagnoses

Diagnosis	NAF		DL	
	N.	%	N.	%
Inadequate	37	45.1	9	13.4
Benign	39	47.6	46	68.7
Mild atypia	5	6.1	9	13.4
Marked atypia	1	1.2	3	4.5
Malignant	0	-	0	-
Total	82	100.0	67	100.0

Discussion

Non lactational secretory activity in the breast may actually be a surrogate marker for proliferative changes in the ductal tissue. These proliferative changes may in turn indicate an increased risk of breast carcinogenesis[5,11]. However, the yield of cellular material from a direct nipple aspirate, is generally too low to permit a meaningful cytological analysis. A major benefit of DL is the substantially improved yield of fluid characterized by a significant cellular content.

To carry out DL, the NAF-producing ducts were cannulated and flushed with saline solution, and the resulting effluent was examined for epithelial cells on which cytopathological analysis was carried out. Cannulation of a fluid-producing ducts is possible in 80% of breasts which produce NAF after manual massage, and is also possible in 90% or more women with spontaneous nipple discharge[5-7, 12].

The distribution of cell types in DL fluid in our study is similar to that in traditional NAF, and includes foam

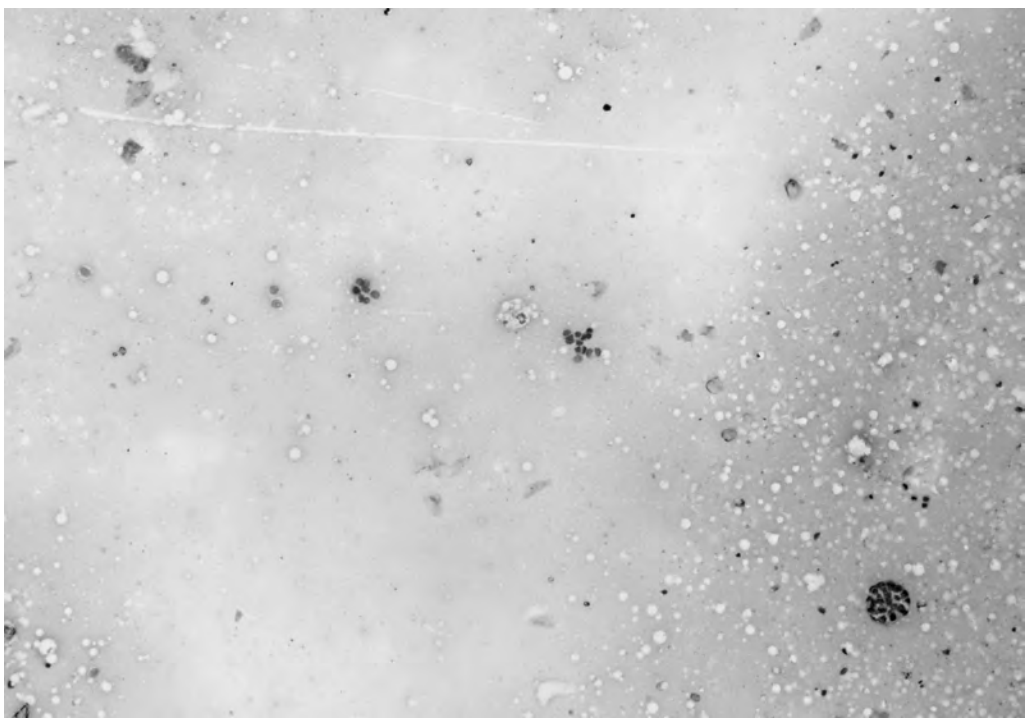

Fig. 1. Benign ductal cells (PAP x 25)

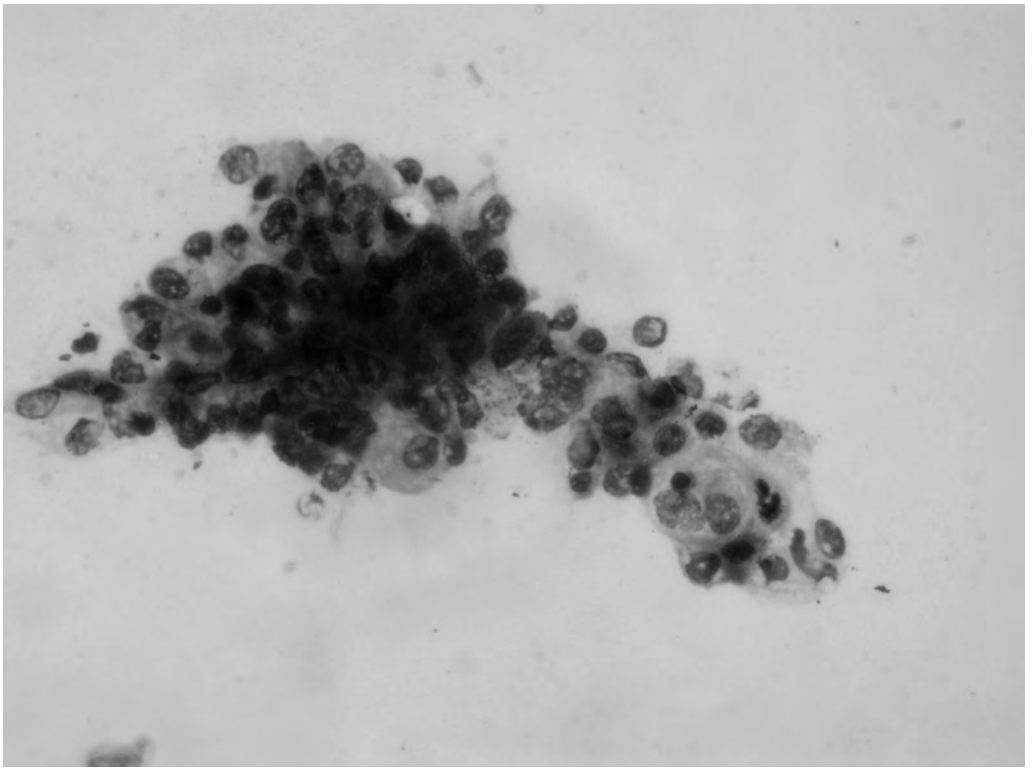

Fig. 2. Mild atypia in a duct group with papillary formation, a feature of intraductal papilloma (PAP x 100)

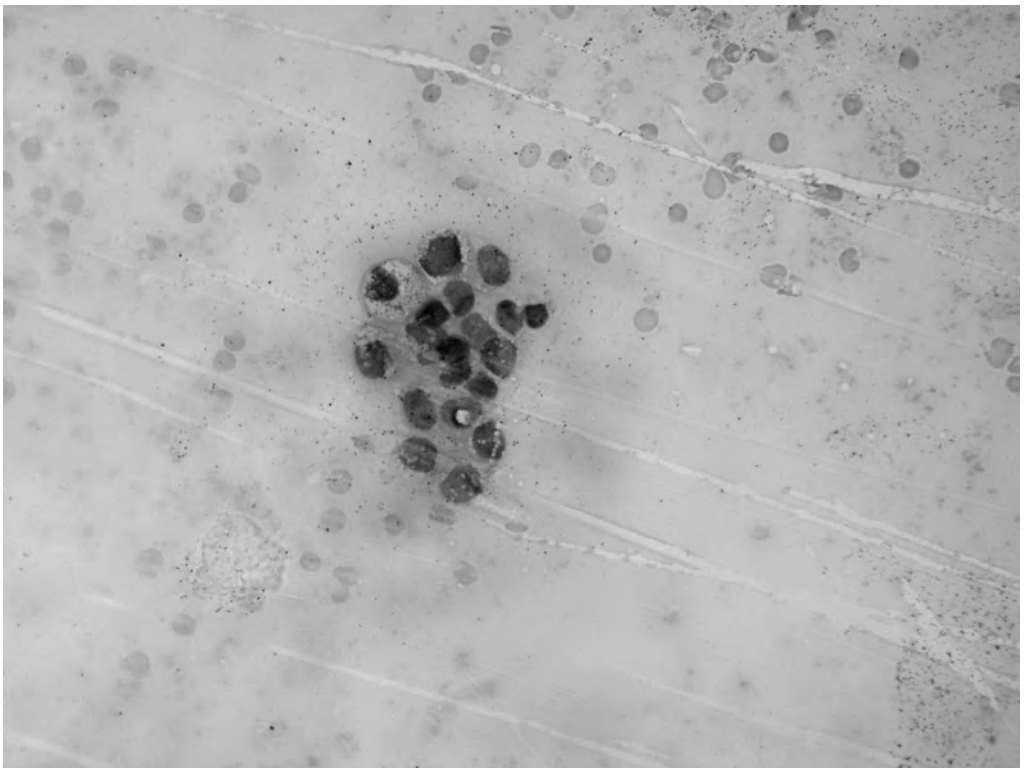

Fig. 3. Marked atypia (PAP x 25)

cells, histiocytes, inflammatory cells and duct cells. Significantly, DL specimens contain a greater number of ductal epithelial cells compared to NAF. Previous investigators have reported similar results[8, 13, 14].

The frequency of atypical cells found by our Institute after DL (17.9%) was higher than that found with the method used until now of non-invasive NAF cytology (7.3%). However, our results were lower than those from the largest research on DL carried out on 383 women, in which atypia was diagnosed in 24% of the studied cases[5].

The frequency of adverse events in our study is similar to that reported by other authors[5, 8, 15].

If a DL specimen contains only benign cells, it is reasonable to repeat the lavage in the same duct at an interval of 1-2 years. Currently benign cytology findings appear to in no way decrease the likelihood of developing breast cancer in a woman considered to be at high risk. Prospective clinical studies are needed to define the optimal interval for repeated lavages and to determine the negative predictive value of DL.

Recommendations for follow up in patients with abnormal DL have been provided by O'Shaughnessy *et al*[16], and Morrow *et al*[17]. Briefly they suggest that these women have an increased risk of developing breast cancer. However no single treatment algorithm will provide the best answer for these cases. Atypia in DL results supports the recommendation of participation in a trial of risk reduction therapy such as the STAR (Study of Tamoxifen and Raloxifen) trial of the US National Surgical Adjuvant Breast and Bowel Project (NSABP)[18], may require more intensive evaluation, including repeated mammography with or without galactography to define the size and location of the ductal system and to exclude filling defects, magnetic resonance imaging, and, if available, ductoscopy. If any suspicious lesions are observed on imaging studies, a biopsy is warranted.

If the cytological examination of a ductal lavage specimen reveals malignant cells (uncommon, less than 1% of high risk women in the study by Dooley *et al*[5]) complementary breast imaging and surgery need to be performed.

Our preliminary results suggest that DL is a safe and minimally invasive procedure that can provide additional information regarding the elevated risk of developing breast carcinoma.

However intraductal approaches to the assessment and management of women patients do not replace mammography screening. Recent publications have demonstrated that DL has a low sensitivity in detecting breast carcinoma[9, 12, 19]. This poor sensitivity of DL for cancer detection could be improved by the use of molecular markers, but significant additional work is required in this area before DL can be considered to be an effective cancer detection tool.

With further refinement of DL and documentation of the delivery of drugs through the ductal system, the intraductal approach for the treatment of breast intraepithelial neoplasia or duct epithelium at high risk could provide clinical benefit with little systemic toxicity.

Finally, despite some limitations, the use of DL for further assessment and management of women at high risk of developing breast carcinoma is a potentially powerful resource, but further studies will be needed to confirm its long-term predictive value.

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Eur. J. Oncol., vol. 10, n. 1, pp. 69-74, 2005

Alterazione dello stato di coscienza in un caso di estesioneuroblastoma olfattorio

Altered consciousness in a case of olfactory aesthesioneuroblastoma

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Riassunto

Descriviamo il caso di una paziente di 73 anni che si presentava con un'iponatriemia inspiegabile associata a disturbi dell'attenzione e della vigilanza ed a rallentamento psicomotorio e dell'eloquio. La TC del cranio evidenziava la presenza di una massa occupante il seno sfenoidale destro. L'esame istologico dimostrava che la lesione corrispondeva ad un estesioneuroblastoma olfattorio. Il caso riveste spiccato interesse per la rarità di questa neoplasia e per i suoi aspetti clinici subdoli ed aspecifici, soprattutto negli stadi iniziali, che rendono la diagnosi alquanto difficoltosa. Eur. J. Oncol., 10 (1), 69-74, 2005

Parole chiave: **SIADH, estesioneuroblastoma olfattorio**

Summary

We report the case of a 73-year-old woman, who presented with an inexplicable hyponatraemia associated with attention and vigilance disorders and slowing-down of psychomotorial function and speech. A CT brain scan showed a mass occupying the right sphenoidal sinus. The histological examination revealed that the lesion was an olfactory aesthesioneuroblastoma. The case is of interest because of the rarity of this neoplasm and its subtle, nonspecific clinical features, especially in the initial phases, which make diagnosis rather difficult. Eur. J. Oncol., 10 (1), 69-74, 2005

Key words: **SIADH, olfactory aesthesioneuroblastoma**

Introduzione

Nell'ambito dei disturbi dello stato di coscienza e vigilanza rientrano quelle condizioni patologiche in cui l'alterazione più o meno importante delle funzioni cognitive è riconducibile a fattori causali ben precisi. Una delle cause è l'encefalopatia secondaria ad alterazioni dell'equilibrio elettrolitico. Essa si presenta con disturbi dell'attenzione e della vigilanza, inerzia, apatia, rallentamento psicomotorio ed ideativo fino al coma. Si possono avere anche manifestazioni psichiatriche (delirio, allucinazioni, depressione, cambiamenti di personalità) e neurologiche (crisi convulsive)[1].

L'estesioneuroblastoma olfattorio è un tumore molto raro, che ha origine dalle cellule olfattive nella cavità nasale[2]. Questo tumore cresce lentamente, soprattutto localmente, anche se le metastasi a distanza non sono inusuali. Le recidive, possibili per tutti gli stadi in una percentuale compresa tra il 38% e l'86% dei casi, si verificano di solito piuttosto precocemente, dopo un intervallo medio di circa 11 mesi[3]. I sintomi conseguenti a tale patologia non sono specifici, ma quelli più comuni sono l'o-

Received/Pervenuto 30.11.2004 - Accepted/Accettato 29.12.2004
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struzione nasale monolaterale e l'epistassi[2]. Talvolta si riscontrano quadri clinici secondari alla produzione di ormoni da parte della neoplasia, etichettabili come "sindromi paraneoplastiche"[4].

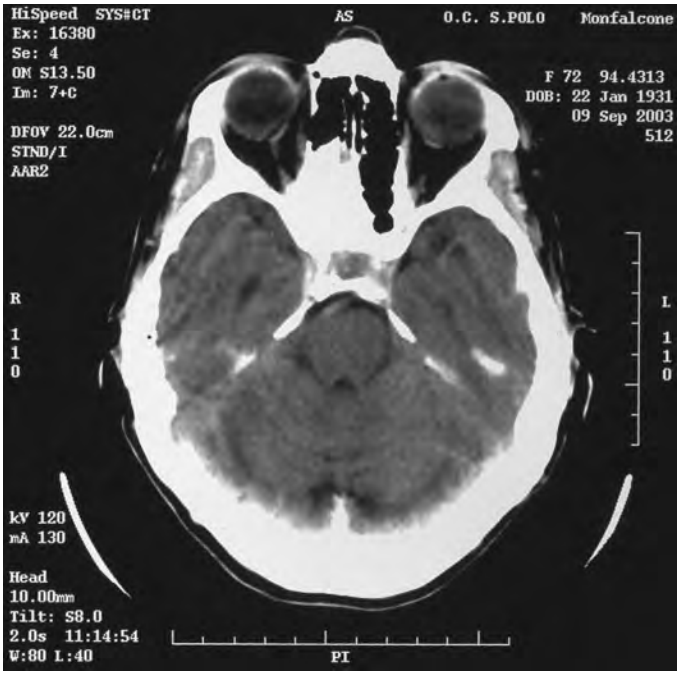
A tale proposito, descriviamo il caso di una paziente con un'iponatriemia inspiegabile che presentava disturbi dell'attenzione e della vigilanza con associato rallentamento psicomotorio e dell'eloquio.

Caso clinico

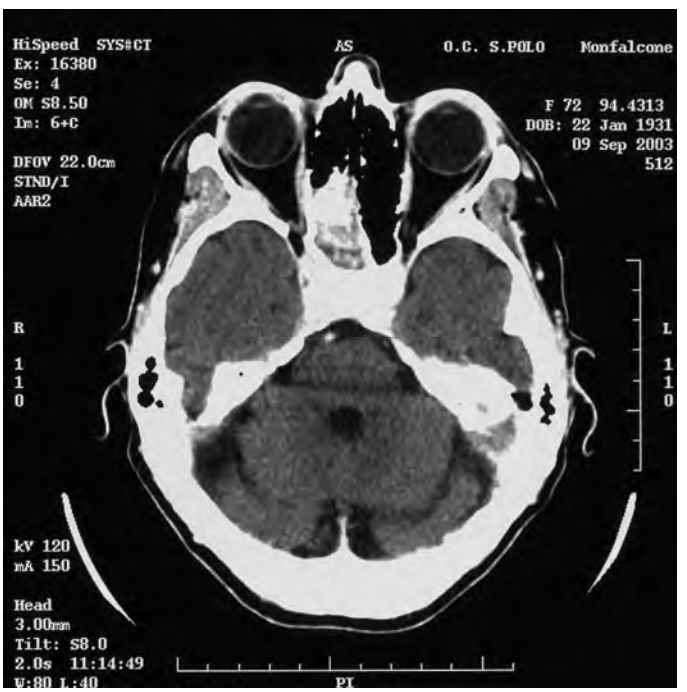
Paziente di sesso femminile, dell'età di 73 anni, che aveva consultato l'internista per astenia, riduzione dell'appetito e conseguente calo ponderale. Anamnesticamente riferiva pregressa agoaspirazione di cisti mammaria bilaterale, asportazione di un polipo benigno del sigma, intervento per ernia jatale, frattura accidentale del piatto tibiale sinistro e dell'omero destro. L'esame obiettivo era sostanzialmente negativo. Si evidenziava però un rallentamento dell'eloquio e della motilità attiva, con spiccata bradicinesia; non deficit di lato; riflessi osteotendinei presenti e simmetrici con riflesso plantare in flessione bilateralmente. I nervi cranici risultavano in ordine. Venivano quindi eseguiti gli esami ematochimici di routine che rilevavano una concentrazione di sodio di 118 mmoli/l (v.n. 133-145), con osmolarità plasmatica ed urinaria rispettivamente di 253 mOsm/Kg (v.n. 278-305) e 553 mOsm/Kg (v.n. 50-1200). Pur non avendo ancora formulato la diagnosi definitiva, è stata instaurata una restrizione idrica che ha comportato un rapido miglioramento del quadro idrico ed umorale. La TC dell'addome superiore evidenziava un fegato lievemente ipodenso; esiti di colecistectomia; pancreas, milza, surreni e reni nei limiti di norma. La TC del cranio non metteva in rilievo alterazioni densitometriche focali delle strutture encefaliche, ma evidenziava la presenza di una formazione iperdensa parzialmente calcifica occupante il seno sfenoidale destro. Uno studio TC successivo, focalizzato a livello sfenoidale, confermava la presenza di una lesione solida iperdensa che, partendo dall'ostio destro, interessava lo spazio del seno sfenoidale allargandone le limitanti scheletriche, in assenza di aree litiche (fig. 1). La lesione solida si espandeva anteriormente a livello delle cellule etmoidali provocando l'assottigliamento delle limitanti scheletriche. Tale lesione veniva meglio definita dalla RMN del massiccio facciale (fig. 2). Si eseguiva, pertanto, una valutazione chirurgica endoscopica in narcosi effettuando un'ampia biopsia della lesione sia a livello endosinusale che a livello della mucosa olfattoria.

L'esame istologico evidenziava una neoformazione costituita da cellule con citoplasma indistinto, nucleo rotondo od ovale con scarse atipie e cromatina fine, con rare mitosi; sostanza intercellulare fibrillare, eosinofila; presenza di alcune pseudorosette. Si osservavano inoltre grossolane calcificazioni stromali amorfe, talora associate a lamine ossee (figg. 3-5). Le cellule neoplastiche erano diffusamente positive per NSE e risultavano associate a elementi dendritici positivi per S-100. La colorazione per neurofilamenti era focalmente positiva. Il quadro istologico corrispondeva a quello di un estesioneuroblastoma olfattorio e, in particolare, il grado istologico corrispondeva al 2° della classificazione proposta da Hyams (Tabella 1)[3,5].

La nostra paziente, clinicamente classificata in stadio B in base al sistema di classificazione proposto da Kadish[3,6], è stata sottoposta a trattamento chirurgico, seguito da radioterapia, con conseguente scomparsa dei sintomi neurologici. Questo fatto conferma l'ipotesi iniziale dell'origine secondaria di questi, dovuta all'interferenza nelle attività metaboliche della cellula nervosa nella corteccia cerebrale e nelle masse nucleari centrali dell'encefalo da parte dell'edema cerebrale. Attualmente, a distanza di circa un anno dal trattamento, la paziente gode di buona salute.



a)



b)

Fig. 1 (a, b). La TC evidenzia una lesione solida iperdensa che interessa l'ostio sfenoidale e che si espande anteriormente a livello delle cellule etmoidali provocando l'assottigliamento delle limitanti scheletriche.

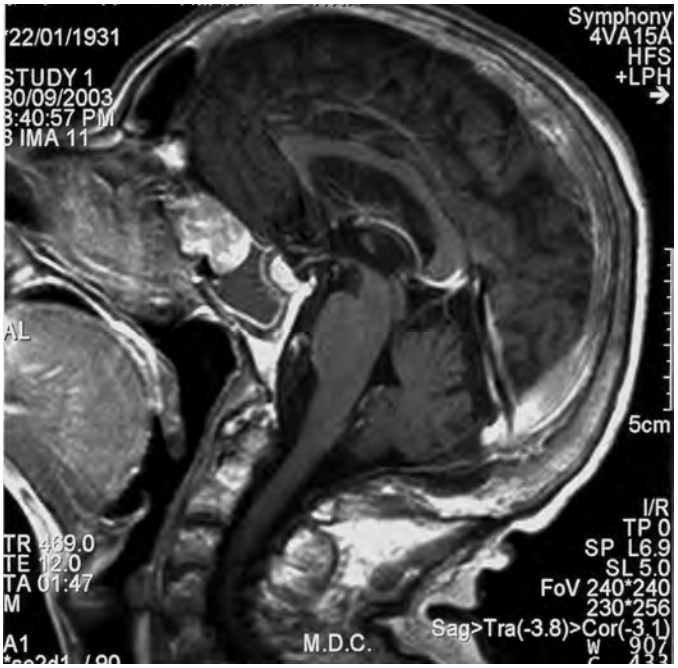


Fig. 2. La RMN dimostra l'interessamento del seno sfenoidale di destra e, in stretta contiguità, del seno etmoidale omolaterale.

Discussione

L'estesioneuroblastoma o neuroblastoma olfattorio rappresenta circa il 5% di tutti i tumori maligni nasali. È stato descritto in soggetti di tutte le età comprese tra i 3 ed i 90 anni, con una distribuzione bimodale dell'età a 20 e 60 anni[2]. È leggermente più frequente nelle femmine. Il tumore origina dall'epitelio olfattorio[7], in cui si riconosce la presenza di tre tipi di cellule: le cellule basali, le cellule olfattorie neurosensoriali e le cellule di sostegno. Le cellule basali sono presumibilmente le progenitrici dell'estesioneuroblastoma. Non si conosce l'esistenza di fattori causali. Non sono state descritte modalità di trasmissione ereditaria né predilezione razziale evidente.

La sintomatologia è piuttosto aspecifica e comune alla maggior parte delle neoplasie naso-sinusali. Proprio per questo motivo, la diagnosi è tardiva e l'intervallo tra il primo segno e la diagnosi definitiva è in genere di circa 6 mesi. I sintomi iniziali sono rappresentati da ostruzione nasale progressiva ed unilaterale, anosmia, epistassi recidivanti. Negli stadi più avanzati, con la progressione locale della neoplasia, compaiono sintomi oculari quali diplopia con rapida proptosi e perdita visiva[2]. L'aspecificità della sintomatologia e del quadro obiettivo rende la diagnosi possibile solo con l'esame istologico su prelievo bioptico.

Microscopicamente, il tumore è caratterizzato da cellule piccole, monomorfe, con nuclei scuri, rotondeggianti ed ovali, con nucleoli poco prominenti e scarso citoplasma a margini sfumati, separate da una matrice fibrillare. Le cellule si dispongono generalmente in aggregati lobulari separati tra loro da uno stroma fibroso riccamente vascolarizzato. Talora le cellule possono essere disposte attorno a capillari formando rosette perivascolari, o attorno a spazi contenenti materiale neurofibrillare costituendo le cosiddette pseudorosette di Homer-Wright. Alcuni tumori contengono vere rosette olfattive tipo Flexner, con lumi ben definiti e delimitati da cellule colonnari che ricordano l'epitelio olfattorio; queste cellule hanno generalmente nuclei basali e si fondono con le cellule adiacenti senza alcuna lamina basale. Le cellule neoplastiche possono

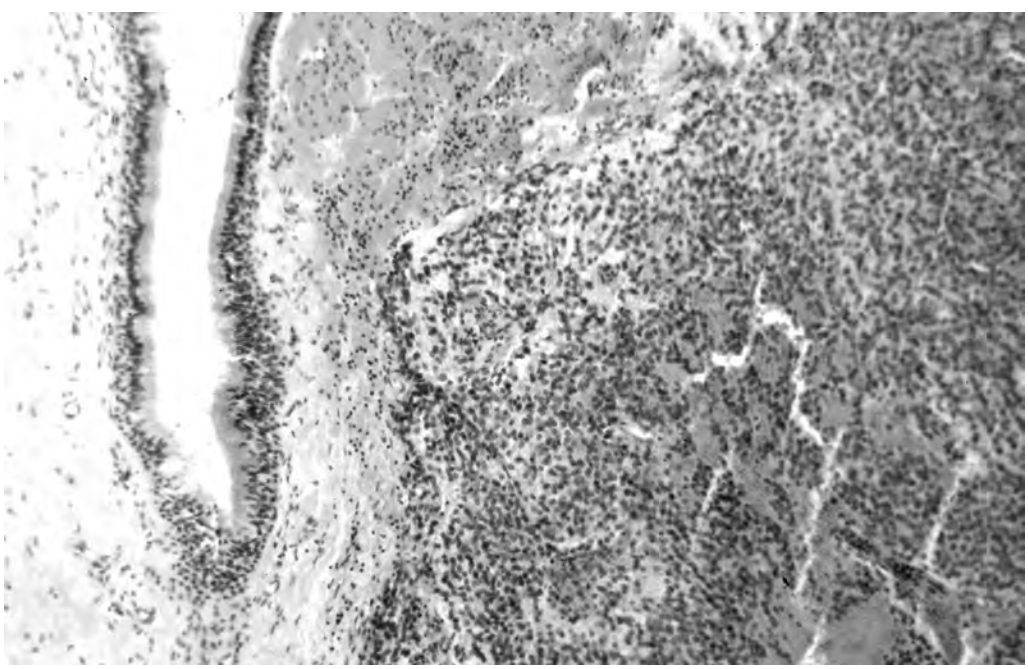


Fig. 3. La mucosa nasale infiltrata dalla neoplasia. EE x 100.

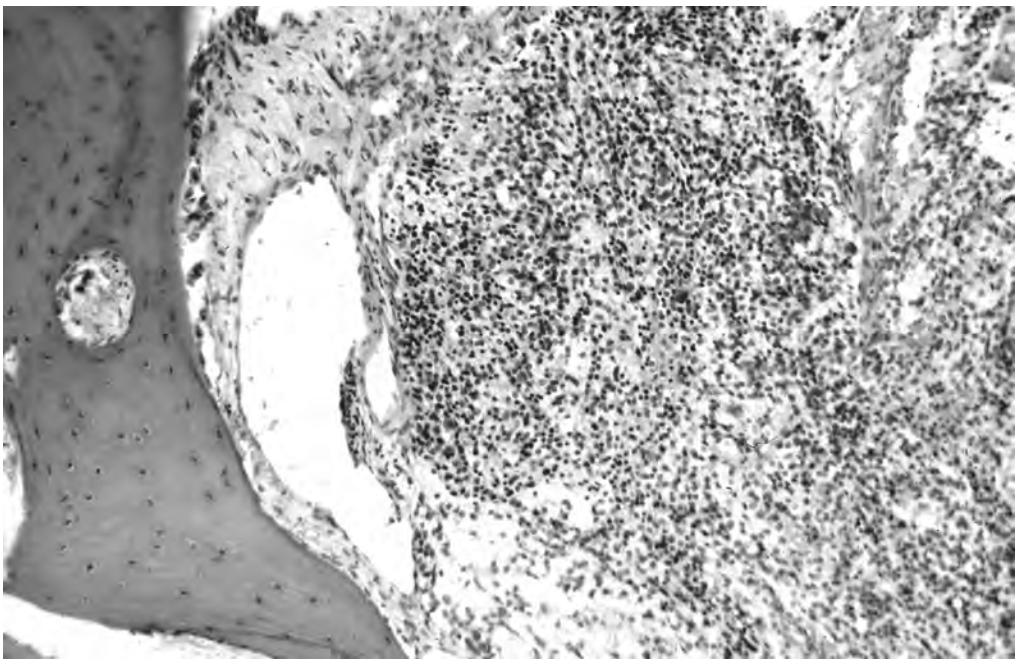


Fig. 4. La proliferazione neoplastica in prossimità dell'osso sfenoide. EE x 100.

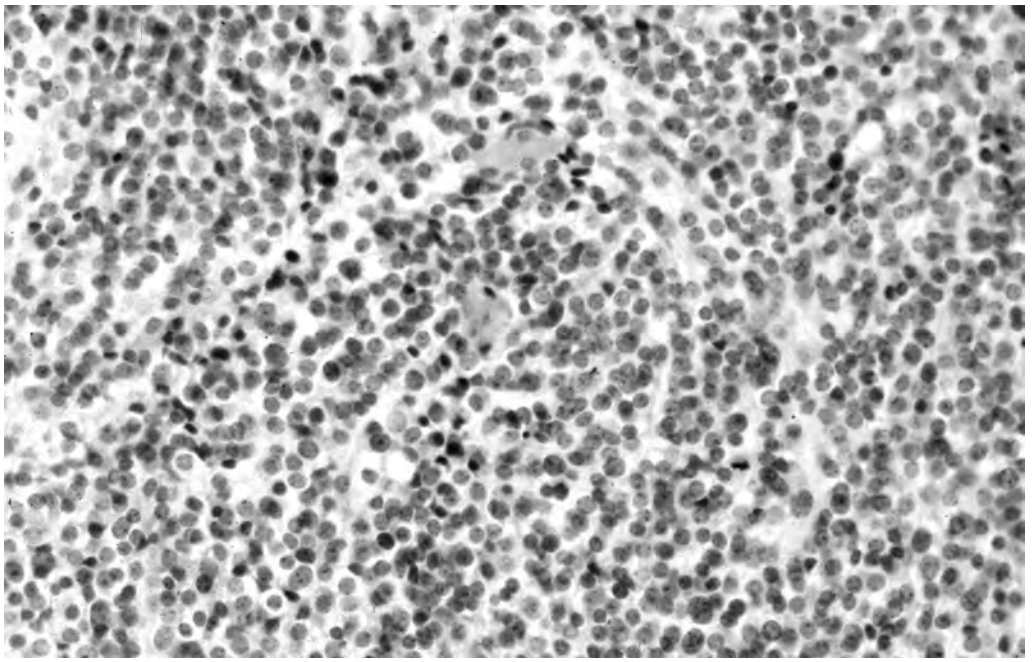


Fig. 5. A maggior ingrandimento, la lesione appare costituita da cellule con citoplasma indistinto, nucleo rotondo od ovale con scarse atipie e cromatina fine. EE x 250.

essere strettamente associate alle componenti epiteliali, superficiali e ghiandolari, della mucosa nasale. Possono essere presenti necrosi e calcificazioni[8].

Anche nel preparato istologico del caso in questione si evidenziava una neoformazione costituita da cellule a citoplasma indistinto, a nucleo rotondo o ovale con scarse atipie e cromatina fine, con rare mitosi; sostanza intercellulare fibrillare, eosinofila; presenza di alcune pseudorosette. Erano presenti inoltre grossolane calcificazioni stromali amorfe, talora associate a lamine ossee.

Il grado istologico dell'estesioneuroblastoma viene stabilito in base alla classificazione proposta da Hyams (Tabella 1)[3] che tiene conto di numerosi parametri istologici della neoplasia: architettura lobulare, indice mitotico, pleomorfismo nucleare, matrice fibrillare, presenza di rosette di Homer-Wright o di Flexner e presenza di necrosi tumorale[2]. Il grado istologico dell'estesioneuroblastoma determina il suo comportamento biologico, in particolare la progressione della malattia, le recidive locali e le metastasi. Le neoplasie di alto grado in base al sistema di Hyams presentano una rapida progressione clinica ed una ridotta sopravvivenza[9]. L'utilizzo di questo sistema classificativo è agevole quando il tumore è ben differenziato, mentre quando il tumore non è differenziato ed

Tabella 1 - Grado istologico secondo la classificazione di Hyams[a]

	Grado 1	Grado 2	Grado 3	Grado 4
Architettura lobulare	Presente	Presente	+/-[c]	+/-
Attività mitotica	Assente	Presente	Rilevante	Marcata
Pleomorfismo nucleare	Assente	Moderato	Rilevante	Marcato
Rosette[b]	H-W +/-	H-W +/-	Flexner +/-	Assente
Necrosi	Assente	Assente	Occasionale	Comune

[a] Grado 1-2: basso grado; grado 3-4: alto grado
[b] H-W: pseudorosette di Homer-Wright
[c] +/-: presenti o assenti

è composto da piccole cellule anaplastiche ipercromatiche che mostrano molte figure mitotiche e scarso citoplasma, la possibilità di diagnosi differenziale da altre neoplasie nasali a piccole cellule diventa difficile. In questi casi, l'estesioneuroblastoma potrebbe essere confuso con altre neoplasie (per esempio il carcinoma indifferenziato nasosinusale, il carcinoma neuroendocrino, il melanoma, il linfoma, il plasmocitoma, il rabdomiosarcoma embrionario, il sarcoma di Ewing, i tumori neuroectodermici primitivi ed i tumori vascolari) e, quindi, la diagnosi viene fatta valutando sia le caratteristiche al microscopio ottico, sia quelle immunoistochimiche, confermate, se necessario, dalla microscopia elettronica[2, 3, 7]. Le colorazioni immunoistochimiche sono utilizzate per individuare marcatori neuronali e neuroendocrini (come l'enolasi neurospecifica, la sinaptofisina, la cromogranina A, i neurofilamenti e la proteina S-100)[8]. Nel nostro caso, le cellule neoplastiche erano diffusamente positive per NSE e risultavano associate a elementi dendritici positivi per S-100.

In alcuni casi, l'estesioneuroblastoma si manifesta dal punto di vista sintomatico con sindromi paraneoplastiche da eccessiva secrezione ormonale[4]. In particolare, la capacità di secernere vasopressina configura la sindrome da inappropriata secrezione di ADH (SIADH)[2, 4, 10-14]. Una SIADH dovrebbe essere sospettata in caso di iponatremia (<l35 mEq/l), osmolarità urinaria (>300 mOsm/Kg) maggiore dell'osmolarità del siero (< 280 mOsm/Kg), peso specifico urinario (>1.015), assenza di edema, ipotensione ortostatica e segni di disidratazione. Una concentrazione di sodio urinaria >20 mEq/l è suggestiva della sindrome.

Nel nostro caso, la concentrazione di sodio era di 118 mmoli/l e l'osmolarità plasmatica ed urinaria risultavano essere, rispettivamente, di 253 mOsm/Kg e 553 mOsm/Kg.

Clinicamente, la sintomatologia è caratterizzata principalmente da segni neurologici dovuti all'edema cerebrale causato dal passaggio di acqua dal compartimento extracellulare, ipotonico, alle cellule nervose. Per queste ragioni, le manifestazioni della SIADH dipendono dal suo grado. In caso di SIADH moderata (concentrazione di sodio serico da 130 a 135 mmol/l, graduale sviluppo nell'arco di alcune settimane), i sintomi possono essere assenti o limitati a nausea, anoressia e vomito. Quando l'iponatremia è grave, o si instaura in modo acuto, i sintomi di tipo centrale sono più importanti e si hanno astenia, letargia, confusione, convulsioni e coma[4].

Nel nostro caso, la paziente presentava un rallentamento dell'eloquio e della motilità attiva, con spiccata bradicinesia.

Il trattamento di queste neoplasie viene generalmente stabilito in base alla stadio clinico, con l'ausilio di tecniche di *imaging* (TC, RMN)[15] e consiste nella combinazione del trattamento chirurgico con quello radioterapico o chemioterapico. Vari sistemi stadiativi sono descritti in letteratura. Il sistema di stadiazione proposto da Kadish è il più comunemente utilizzato e consta di tre stadi: stadio A (neoplasie confinate alla cavità nasale), stadio B (neoplasie coinvolgenti i seni paranasali) e stadio C (tumori che si estendono oltre i limiti della cavità naso-sinusale, ad esempio cavità cranica o orbitaria). Foote[16] ha modificato il sistema Kadish aggiungendo uno stadio D che include le metastasi ai linfonodi cervicali o a distanza. Altri sistemi stadiativi clinici, basati sul sistema TNM, sono stati proposti da Dulguerov e Calcaterra[3, 9, 17]. In letteratura non c'è alcun consenso sul sistema di stadiazione clinico più appropriato[9]. In base alla stadiazione di Kadish, i pazienti con malattia localizzata, cioè in stadio A, vengono trattati chirurgicamente. L'associazione con la radioterapia è da preferire se, con la resezione locale, non sono stati ottenuti margini sicuri. L'associazione della chirurgia e della radioterapia adiuvante si rende obbligatoria per i pazienti in stadio B, mentre la chemioterapia viene utilizzata in prima battuta nei pazienti in stadio C, combinata ad ampie resezioni chirurgiche ed alla radioterapia. La maggior parte dei dati recenti segnala un tasso di sopravvivenza, a cinque anni, variabile dal 52% al 90%, e nel 38-86% dei casi le recidive si hanno in media entro 11 mesi dopo il trattamento per tutti gli stadi[3].

Conclusioni

Il caso da noi descritto riveste spiccato interesse per la rarità della forma oncologica (1000 casi sono stati riportati in letteratura dopo la prima descrizione di questo tipo di neoplasia fatta da Berger nel 1924[2, 18]) che, unitamente alla clinica particolarmente subdola ed aspecifica negli stadi iniziali, ne rende la diagnosi alquanto difficoltosa. Nella pratica clinica è indispensabile eseguire sempre un'indagine rapida e sistemica del paziente che presenta un disturbo della coscienza. I sintomi neurologici, infatti, possono a volte essere significativi e ricchi di informazioni. In questo caso, il riconoscimento della sindrome neurologica ha portato alla diagnosi di SIADH, avvalorata dalla risposta positiva alla restrizione idrica considerata criterio *ex adiuvantibus*. La terapia da intraprendere per quella che si presentava come una malattia neurologica, rientra pertanto nel campo della medicina interna.

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