EUROPEAN JOURNAL OF ONCOLOGY

GIORNALE EUROPEO DI ONCOLOGIA

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

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

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

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

INDICE/CONTENTS

VOLUME 8 - N. 1 - 2003

ARTICOLI SU STUDI E RICERCHE ORIGINALI / *ARTICLES ON ORIGINAL STUDIES AND RESEARCH*

Eur. J. Oncol., vol. 8, n. 1, pp. 7, 2003

XXVIII Congresso Nazionale di Oncologia della SIT - Torino, 28-30 novembre 2002

Allocuzione del Presidente Onorario della Società Italiana Tumori alla cerimonia inaugurale del Congresso Interdisciplinare della Società Italiana Chirurghi Universitari e della Società Italiana Tumori

XXVIII National Congress of Oncology of the SIT - Turin, 28-30 November 2002

Address of the Honorary President of the Italian Society for Tumours at the opening ceremony of the Interdisciplinary Congress of the Italian Society of University Surgeons and the Italian Society for Tumours

Professor LEONARDO CALDAROLA

Signor presidente del Congresso, autorità, gentili signore e signori, cari colleghi,

quale presidente onorario e decano della Società Italiana Tumori (SIT) rivolgo a tutti voi il mio personale saluto.

Come è stato ampiamente chiarito nella presentazione del programma scientifico congressuale, ed ancor meglio dagli interventi che abbiamo ascoltato, il XXVIII Congresso della SIT, pur conservando la sua linea tradizionale di polidisciplinarità, rafforza oggi ulteriormente questa sua vocazione integrandosi con il 1° congresso della Società Italiana Chirurghi Universitari (SICU): questo alla luce delle nuove realtà e strategie richieste dalla formazione, dal progresso tecnologico e da quello, ancor più tumultuoso, della ricerca in questa era genomica e post-genomica che tutti viviamo, che richiedono orientamenti e risorse non ulteriormente differibili.

Tali temi saranno dibattuti da autorevoli relatori nel primo congresso SICU, come pure, nello stesso ambito, saranno discussi interessanti argomenti di clinica e di terapia chirurgica.

Ne consegue che la scelta di un congresso interdisciplinare, adottata dagli organizzatori, rafforza quei criteri a cui si è uniformata la SIT fin dalla sua fondazione, e cioè una società scientifica aperta ad esperti di diversa formazione e provenienti da università, ospedali, centri e istituzioni oncologiche cliniche e di ricerca, nel rispetto della specifica competenza e caratterizzazione professionale dei singoli.

Merita altresì apprezzamento che nel programma scientifico sia stata opportunamente prevista una tavola rotonda dedicata alla promozione di "federazioni intersocietarie", eventualità questa auspicata da parte di molti, al fine di un più organico e tempestivo scambio culturale e scientifico.

La SIT, d'altronde, in ordine alle sue linee programmatiche e fin dalla sua costituzione, ha sempre cercato di privilegiare le finalità anzidette sia con la costituzione di comitati di studio, sia nell'impostazione delle sue attività congressuali nazionali e regionali.

Desidero ora a titolo personale, ma credo anche interpretando il pensiero dei presenti, compiacermi con il Professor Mussa per l'impegno ed il coraggio posti per la realizzazione dei due importanti eventi scientifici, in un momento di particolare difficoltà economica per il nostro Paese e particolarmente per il Piemonte.

L'aiuto provvido, come il Professor Mussa ci ha detto, è venuto pressoché totalmente dagli Enti Istituzionali, che hanno dimostrato sensibilità sociale e considerazione non comune nei confronti dei settori della ricerca e del progresso tecnologico, ai quali si improntano, d'altronde, i contenuti scientifici dei due congressi. Ciò non toglie, tuttavia, che la realizzazione di questa importante assise, che onora la nostra città, la si deve anche alla stima che circonda il Presidente Mussa, i componenti dei Comitati organizzatori e quanti hanno con loro collaborato. Complimenti quindi ed auguri di pieno successo per i lavori congressuali ed auguri, altresì, di lieto soggiorno a tutti gli intervenuti.

Eur. J. Oncol., vol. 8, n. 1, pp. 9-16, 2003

Ricordo del Professor Cesare Maltoni, nel secondo anniversario della sua scomparsa / *Commemoration of Professor Cesare Maltoni, in the second anniversary of his death*

Cesare Maltoni: his life and accomplishments

Cesare Maltoni: la vita e le opere

Myron A. Mehlman
Department of Environmental Medicine, Mount Sinai School of Medicine, New York, NY, USA

Introduction

Professor Cesare Maltoni (fig. 1), a worldwide renowned leader in the research of chemical hazards of industrial carcinogens in the workplace and environment, died on January 22, 2001 at the age of 70. Born on November 17, 1930, he was raised in Faenza (Ravenna), Italy. In 1955, he received his medical degree from the University of Bologna, Italy. From 1957-1958, he was a fellow at the Curie Foundation in Paris, where he worked with Professor A. Lacassagne and Professor R. Latarjet. From 1959-1961, Maltoni was a Research Associate at the Department of Cancer Research of Michael Reese Hospital and Medical Center in Chicago with Dr. A. Tannenbaum. From 1961 to 1964, he worked with Professor E. C. Vigliani at the Clinic for Occupational Diseases of the University of Milan. In 1964, he became Director of the Institute of Oncology of Bologna. From 1966, he was Professor of Experimental Oncology. From 1966 to 1989, Professor Maltoni was also Director of the Bologna Centre for the Prevention and Detection of Tumours and Oncological Research. He was Professor at the Post Graduate School of Oncology of the University of Bologna since the foundation of the school in 1978. From 1989 until the time of his death, he was Director of the European Foundation of Oncology and Environmental Sciences "B. Ramazzini".

Professor Maltoni's contributions to research and causation of cancers dealt with the carcinogenicity of many compounds. In the Cancer Research Centre of the Castle of Bentivoglio (fig. 2) he conducted long-term carcinogenicity studies on almost 200 agents, and he was the first to demonstrate that vinyl chloride is a carcinogenic agent producing, among others, angiosarcomas of the liver. He was the first to demonstrate that benzene is a powerful multipotential carcinogenic chemical. He was a member and officer of many National and International scientific organizations and advisory boards and received world-wide recognition for his accomplishments. Professor Maltoni, along with his associates, published over 700 scientific articles. He was a person of great stature and many accomplishments and will never be forgotten.

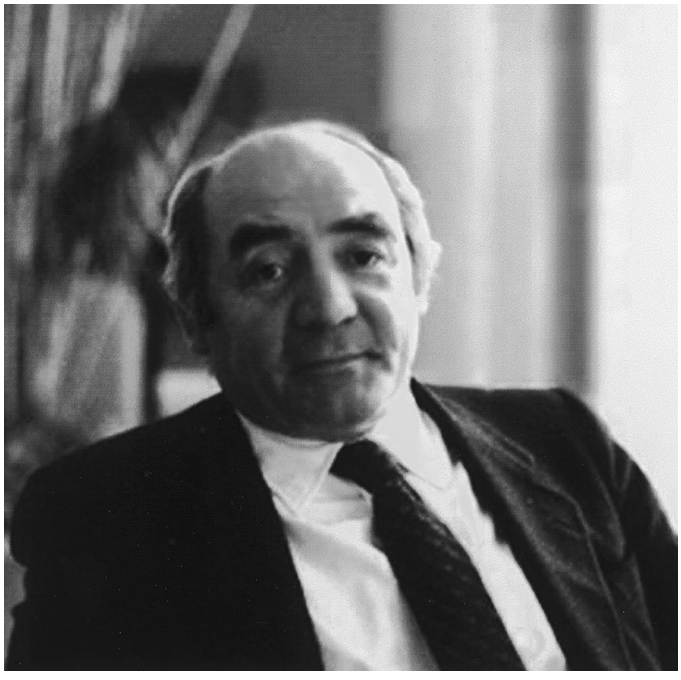

Fig. 1. Professor Cesare Maltoni (1930-2001)

"I wish you to know
that in this terrible moment,
the only message a friend can convey
is that you must remember
when we all were happy together."

- Cesare Maltoni

Background and history

Cesare Maltoni was born in Faenza (Ravenna), Italy on November 17, 1930, to Maria Porisini Maltoni and Carlo Maltoni.

Pervenuto/Received 10.10.2002 - Accettato/Accepted 29.11.2002
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Fig. 2. The Castle of Bentivoglio, where the research of Cesare Maltoni continues in the Cancer Research Centre of the European Ramazzini Foundation

Fig. 3. Cesare Maltoni and Professor Favilli, his advisor, at the time of awarding of the M.D. degree from the University of Bologna in 1955

Maltoni graduated from the University of Bologna in 1955, where he received his medical degree. He and his advisor, Professor Favilli, are shown in fig. 3. Maltoni's experimental thesis was entitled: "Changes in the dermis during experimental skin carcinogenesis". Maltoni's parents died when he was still a young man; he was cared for all of his life by his aunt, Afra Maltoni (fig. 4) of Faenza, Italy. Throughout his life, he visited his aunt frequently in Faenza where he also owned an historic house.

Career highlights

Throughout his professional life, Maltoni received many professional and scientific appointments, honors and held many positions. He served as:

– Secretary General of the Collegium Ramazzini, an International Academy consisting of 180 members who are experts on the relationship between cancer development, environment, work and health, since its foundation in 1982;
– Past President (1981-1986) and Honorary President (1986-2001) of the Italian Society for Tumour Prevention, Diagnosis and Therapy;
– Past Chairman of the International Committee for Human Tumour Investigation;
– Member of the Italian National Board of Health (1984-1989);
– Member of the National Commission for Mutagenesis, Carcinogenesis and Teratogenesis of the Italian Institute of Public Health (now National Commission of Toxicology) from 1975-1989;
– Member of the Académie Internationale de Lutuèce;
– Member of the Académie Européenne des Sciences des Arts et des Lettres;
– Member of the National Technical Scientific Commission for Biosafety for evaluation of potential health risk from genetically modified organisms, Italian Ministry of the Environment in 2000;
– National Chairman of the Environmental and Occupational Carcinogenesis Committee set up in 2000 by the Italian League for the Fight against Cancer.

For his work, Maltoni received many awards. But a few are:

– the Golden Medal "Faentino Lontano" of the town of Faenza (Faenza, 1974);
– the International Award for Cancer Prevention of the Italian League for the Fight against Cancer of Latina (Latina, 1994);
– the Stokinger Award of the American Conference of Governmental Industrial Hygienists (ACGIH) (Kansas City, 1995);
– the International Award "B. Ramazzini" of the Collegium Ramazzini (Washington, DC, 1995);
– the International I.J. Selikoff Memorial Award (Washington, DC, 1995);
– the Sigillum Magnum of the University of Bologna (1997);

Fig. 4. Afra Maltoni, Cesare Maltoni's aunt, who raised him and was a tower of strength throughout his life

– the Golden Medal of the Italian Society of Tumours (SIT) Prevention, Diagnosis, Therapy (Bologna, 2000) (fig. 5).

Professor Maltoni's legacy and major scientific contributions include the following:

– establishment of the relevance of connective tissue changes in the carcinogenesis and natural history of tumours and metastasis formation;
– pioneering the use of animal models for the identification of environmental carcinogens, the assessment of carcinogenic risks, and the evaluation of tumour chemopreventive compounds;
– documentation of the multipotential nature of a large number of carcinogenic agents;
– establishment of the carcinogenicity of several important industrial agents including vinyl chloride, vinylidene chloride, acrylonitrile, trichloroethylene, formaldehyde, gasolines, gasoline aromatics and MTBE;
– documentation of high oncogenic risk due to exposure to asbestos used in the railroad and in the sugar industries;
– establishment of the Nominative Bologna Registry of Mortality with particular regard to cancer;
– direction of screening of 270,000 women for early diagnosis of uterine cervical cancer and 125,000 women for early diagnosis of breast cancer;
– creation of the first Italian hospice for terminal cancer patients.

Occupational carcinogenesis

In 1973, Professor Maltoni convened a major symposium in Bologna, Italy on the topic of "Advances in Tumour Prevention, Detection and Characterization". In fig. 6, Maltoni and Lanfranco Turci, President of Emilia Romagna Region, welcome distinguished scientists from all over the world who participated in this major symposium. The proceedings of this conference were published in 1974 in Excerpta Medica.

Maltoni was known for his meticulous and carefully documented experiments. He studied 198 chemicals and agents and conducted 394 separate experiments using 138,281 animals. Of the 135 agents studied, 68.9% were found to be carcinogenic and

Fig. 5. Cesare Maltoni receives the Golden Medal of the SIT from Professor Leonardo Caldarola, co-Honorary President of the SIT

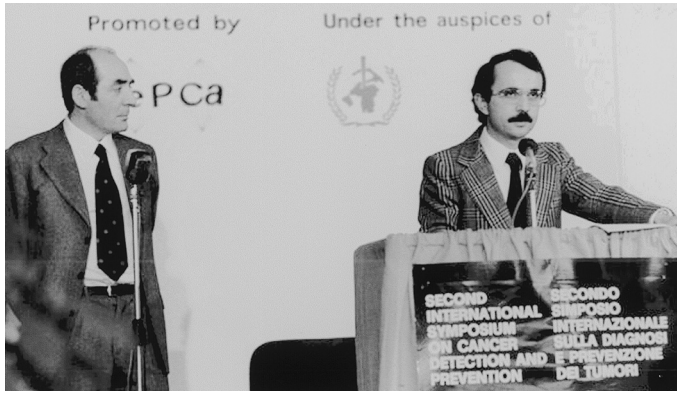

Fig. 6. Cesare Maltoni and Lanfranco Turci, President of the Emilia Romagna Region, at the symposium in Bologna in 1973

5.92% showed borderline carcinogenicity; 25.18% were found to be non-carcinogenic in the animals tested.

Professor Maltoni authored and co-authored more than 700 original scientific publications, numerous books and proceedings in the National and International literature, and was Editor and Co-editor of many journals.

Maltoni's studies resulted in scientific publications of major significance, some of which included carcinogenesis of vinyl chloride[1], of vinylidene chloride[2], and trichloroethylene[3].

Vinyl chloride carcinogenesis

Maltoni's study of the carcinogenicity of vinyl chloride began in 1971 and lasted until 1983[1]. It included more than 7,000 animals, the majority of which were submitted to chronic treatment; all were kept under observation until spontaneous death; more than 200,000 histological slides were examined. To our knowledge, these studies are the largest ever performed in carcinogenesis in one laboratory on a single industrial compound.

This project produced a good deal of important information:

– it clearly demonstrated that vinyl chloride is a carcinogen that produces a variety of tumours in different tissues and organs;
– it indicated that liver angiosarcoma is the most specific marker of vinyl chloride-related tumours;
– it promoted the epidemiological investigations that led to the discovery of liver angiosarcomas in vinyl chloride-exposed workers;
– it produced dose-response data, thereby providing the scientific basis for regulatory measures;
– it provided the scientific proofs that long-term carcinogenicity bioassays can predict oncogenic risk for humans and can be the basis for quantitative risk assessment.

Maltoni's studies on vinyl chloride:

– led to the control of vinyl chloride exposure;
– promoted carcinogenicity studies of numerous chemically correlated compounds to assess their potential risk;
– stimulated national and international regulations for the control of environmental toxic agents including the passing of legislation requiring pre-production testing;
– constituted a model for research protocols in the field of occupational and environmental carcinogenesis, including a

large part of those contained in the Good Laboratory Practice Acts for long-term carcinogenicity bioassays;
– demonstrated that experimental findings can be extrapolated to human pathology in the area of potential carcinogens;
– contributed to basic knowledge of factors and mechanisms of carcinogenesis;
– demonstrated that studies in the field of environmental and occupational carcinogenesis must no longer be considered retrograde ancillary research, but that such studies must be an important component in the decision-making process.

Trichloroethylene carcinogenesis

Maltoni's studies on the carcinogenicity of trichloroethylene (TCE) began in 1976[3]. These studies employed 3,948 animals of different species and strains. In all experiments but one, animals were submitted to TCE by inhalation. All animals were kept under observation until spontaneous death. To our knowledge, this experimental project is the largest performed on TCE carcinogenicity.

This project provided the following information on TCE:
– TCE is carcinogenic in two different strains of mice;
– TCE causes tumours in rats;
– renal lesions and tumours in rats are the most specific marker of TCE-correlated pathology.

Under the experimental conditions, the evidence of TCE (without epoxide stabilizer) carcinogenicity is based on the following results:

1) following long-term inhalation exposure:
– TCE caused an increase in hepatomas in male Swiss and B6C3F1 mice;
– TCE caused lung tumours in male Swiss and female B6C3F1 mice;
– a dose-related increase in Leydig (interstitial) cell tumours of the testes was observed in Sprague-Dawley rats;
– there is some evidence that TCE produced an increase in the incidence of leukaemias (mainly immunoblastic lymphosarcomas) that was not dose-related;
– TCE induced the onset of a few characteristic kidney tubular adenomas in males at the highest dose tested;

2) following ingestion exposure:
– a borderline increase in leukaemia was observed in male rats.

Significance of Maltoni's protocols

There is a concept of which Maltoni was particularly fond: "Is the glass half empty or half full?" Maltoni's experimental protocols were designed to answer that question.

Typically, industry conducted or sponsored long-term oncogenicity studies that were generally designed not to completely answer the question of whether the glass was half full or half empty. In order to introduce disputes as to the question of carcinogenicity of a compound, the studies consistently were conducted by giving animals at least one very high dose of the compound being tested, often 8,000 ppm, which is a magnitude greater than humans would be exposed to. This provided an argument that humans are never exposed to these levels of doses, and results could not be applied to humans.

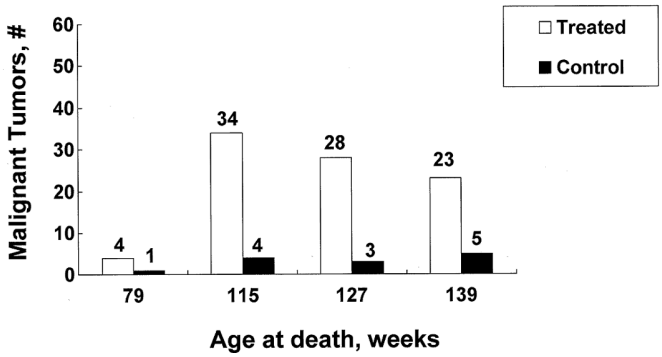

Fig. 7. Life span studies of the appearance of malignant tumours in animals exposed to xylene

Legator[4,5] demonstrated that for benzene, vinyl chloride, and butadiene, high doses greatly underestimated the carcinogenic risk to humans. In addition, in the US EPA and FDA ED_{01} study, Staffa and Mehlman[6] published a major study using 24,192 animals. The study showed that there is no safe level for carcinogens and that no dose above zero is without risk. These studies refuted the fallacious argument, which is still today being used, by industry health professionals and their consultants, to defend potentially carcinogenic products and to not really reach an answer.

The second technique generally supported by industry was to limit the time of animal exposure to potential carcinogens to two years or less. By imposing this limitation, the real risk of carcinogenicity of a compound could be substantially underestimated and, in some cases, totally missed. In fig. 7, the effect of extending the length of the experiment to more fully determine carcinogenicity during the life span of the animal shows the carcinogenic effect of xylene revealed in the period of time after the usual 2-year cut-off period.

The third method used by some manufacturers of potentially carcinogenic products was to attack the messenger. Maltoni's meticulously conducted experiments and experimental goals made such attacks frivolous. In particular, the duration of Maltoni's experiments more closely paralleled human experience in that tumours often develop not in the prime of life but later as the individual ages. This medical concept cannot be challenged. Therefore, Maltoni's goals in studying the carcinogenicity of chemicals were:

– to identify new potential carcinogenic materials;
– to evaluate the effects of technological modifications of already demonstrated carcinogenic materials with the aim of lowering their risk;
– to assess, in quantitative terms, the relative carcinogenic risk of different materials with particular regard to alternative choices, and to guide the formulation of future materials and choices;
– to help to predict the target organs;
– to define the carcinogenic potential of the physical and chemical properties of the test compounds;
– to determine the rôle of different biological and experimental factors affecting the neoplastic response and, consequently, to shed light on the mechanism of the possible oncogenic effects of compounds found or suspected to be carcinogenic;
– to help trace the natural history of tumours induced by the test compounds;

Fig. 8. First meeting of Fellows of the Collegium Ramazzini in 1983. Fellows present are as follows: Seated: Cesare Maltoni, Werther Cigarini, former Mayor of Carpi, and Irving J. Selikoff. Standing: Muzaffer Aksoy, Giuseppe Paladini, Jorge Chiriboga, Vito Foà, Giovangiacomo Giordano, Jerry Stara, Myron Mehlman, Bo Holmberg, Sheldon Samuels, John Harington, Ruth Lilis, Pericle Di Pietro, Elihu Richter

– to conduct experiments at low levels of exposure; and
– to carry out experiments for extended periods of time, often as long as 30-36 months, basically for the lifetime of the animal.

The Collegium Ramazzini

For the major part of his life, Professor Maltoni was dedicated to the philosophy of Bernardino Ramazzini, a philosophy that spawned the Collegium Ramazzini. Bernardino Ramazzini[7] was an 18th century physician and scholar who realized the link between occupational exposure to dangerous chemicals and conditions and adverse effects on workers' health.

The Collegium Ramazzini was organized as a non-profit organization dedicated to detecting adverse working conditions and chemical exposures and improvement of working conditions and minimizing danger of such exposure to workers. Along with giants in epidemiology, environmental health and occupational health, including Norton Nelson and Irving J. Selikoff, Maltoni devoted much of his life to the protection of workers. In this light, Selikoff, Maltoni, Mehlman, and Samuels founded the Collegium Ramazzini, an organization of international health professionals dedicated to improving environmental and occupational health.

During his lifetime, Maltoni worked, travelled and participated in the development of policy with Fellows of the Collegium from 35 countries who were leaders in the fields of occupational and environmental health, labour, and public policy. The first meeting of the fledgling "Collegium Ramazzini" was held in Carpi, Italy in 1983. A photograph of many of the initial Fellows of the Collegium Ramazzini is shown as fig. 8. The City of Carpi, home of Bernardino Ramazzini, has served as the annual meeting place of Fellows of the Collegium Ramazzini for nearly 20 years and will do so for years to come, largely due to Professor Maltoni's efforts and stature in the scientific community.

History and memories of meetings of the Collegium Ramazzini are immortalized in photographs taken in Italy, the USA, Japan, and many other countries (figs. 9-16). These photographs are a tribute to Maltoni's memory and to his close friends and colleagues who worked both directly and indirectly to promote public health, safety of the workplace, and the environment.

Fig. 9. Myron Mehlman and Cesare Maltoni

Fig. 10. Franco Pannuti, Senator Luigi Orlandi, former President of the Italian Ramazzini Institute, Cesare Maltoni and Massimo Crespi at the Fifth International Symposium on the Biological Characterisation of Human Tumours, Bologna, April 1973

Fig. 11. Marina Thorborg, Irving J. Selikoff, Cesare Maltoni, Nicholas Ashford, Eula Bingham and Philip J. Landrigan in Japan

Fig. 12. Cesare Maltoni and Claudio Bergianti, former Mayor of Carpi, Ramazzini Days in Carpi, 1992

Conclusion

Professor Maltoni was a true friend of working men and women. The effects of Professor Maltoni's lifetime work and

Fig. 13. Cesare Maltoni, Luigi Orlandi and Irving J. Selikoff in New York City

achievements place him in a very small and select group of world scholars the likes of Ramazzini and Hippocrates. Not only was Maltoni one of the greatest experimental oncologists, he was also a physician who made important medical and oncological re-

Fig. 14. Luigi Orlandi, Irving J. Selikoff, Cesare Maltoni and Myron Mehlman at the Castle of Bentivoglio

Fig. 15. Drs. Mehlman, Dr. Soffritti and Mr. Malavasi, present Mayor of Carpi, plan for continue support of the Collegium Ramazzini by the Town of Carpi

Fig. 16. Prefetto Rossano of Bologna, Prof. Irving J. Selikoff, President of Collegium Ramazzini, Prof. Fabio Roversi Monaco, Rector of the University of Bologna, Renzo Imbeni, Major of Bologna, Dr. Oakes Ames, President of the New York Academy of Sciences, Prof. Angelini, Accademia dei Lincei, and Prof. Cesare Maltoni at the Convocation of World Academies, Bologna, 1989

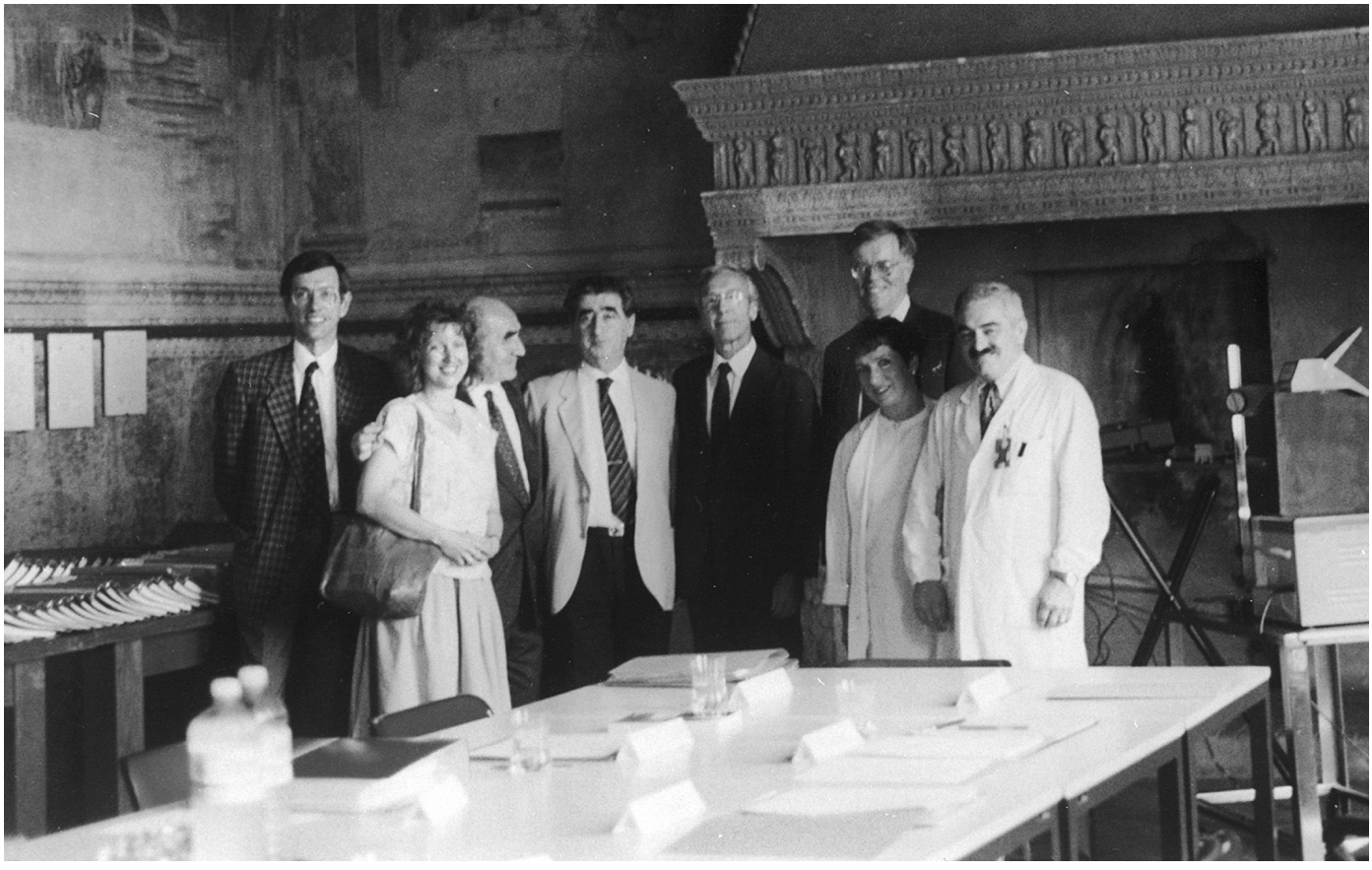

Fig. 17. Meeting at the Ramazzini Foundation Cancer Research Centre, Castle of Bentivoglio, July 1994. From the left: Dr. Franco Minardi, Dr. Jill V. Brazier, Prof. Cesare Maltoni, Prof. Vito Foà, Prof. Arthur C. Upton, Prof. David G. Hoel, Dr. Fiorella Belpoggi, Dr. Morando Soffritti

search contributions. And most importantly, just as Professor Irving J. Selikoff, who was a close colleague and personal friend of Professor Maltoni, he was a teacher who practiced Ramazzini's philosophy that "it is better to prevent than to cure".

Gentleness, kind-heartedness, helpfulness in the cause of the underdog: these were human qualities that are associated with him. Yet he could be firm, not to say scathing, in the face of arrogance, posing, opportunism or off-handedness. He was a man of finesse and culture, a lover of art, literature, and poetry. He seemed to possess a key to these, based on an uncommon respect for fine detail.

To his close co-workers, he leaves works, actions, projects and culture, but above all a spirit he doggedly sought to instill: a sense of mission, the determination to carry it out, and "the habit of telling the truth, come what may".

Many of us fellow Ramazzinians and his coworkers (fig. 17), wish to be considered as a part of group, as he once wrote, of his "always family friends" and to remember happy moments when we were together. We will remember Professor Maltoni's devotion of his life, his energy, and his love of saving lives for the betterment of mankind. A man of great stature and many contributions, he will never be forgotten.

Acknowledgements

Special thanks are due to Morando Soffritti, Fiorella Belpoggi, Donata Carretti, Giorgio Perino, Renzo Dal Zotto for their assistance in providing background material and critiquing this manuscript and to my wife, Karyl Norcross Mehlman, M.D., Ph.D., for preparation of all graphic materials.

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Eur. J. Oncol., vol. 8, n. 1, pp. 17-20, 2003

Editoriale/Editorial

Perspectives of hypoxia in anticancer treatments: activated prodrugs and bioreductive perfusions

Pro-farmaci attivati in condizioni di ipossia e perfusioni con agenti bioreduttivi: ruolo nella terapia medica dei tumori

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Summary

Tumour hypoxia is a limiting factor in both the radiotherapy and chemotherapy of solid tumours. Paradoxically it is also an attractive therapeutic target, because significant hypoxia occurs only in solid tumours. Hypoxic cells can be considered for therapy by non-toxic, hypoxia-activated prodrugs. Conceptually, "trigger" units in these drugs are selectively activated in hypoxic cells to release or activate a toxic "effector", capable of killing surrounding oxygenated tumour cells. Useful triggers include quinones, nitroaromatics, N-oxides, and transition metals. At present the N-oxide tirapazamine (TPZ) is in phase III clinical trials. Solid tumour tissue is poorly perfused compared with normal tissue. Reasons include a rather limited, poorly structured, and inefficient tumour vascular supply, and high interstitial pressures. This leads to variable delivery of oxygen, other nutrients and drugs, resulting in regions of hypoxia (oxygen partial pressures of <5-10 mm Hg) in many human solid tumours. This hypoxia can be classified into three broad types: a) chronic or diffusion hypoxia keeps cells, that are sufficiently distant from the nearest blood capillary, hypoxic for long periods; b) transient or perfusion hypoxia results from the temporary shutdown of blood vessels, placing areas of tissue under hypoxia for shorter periods; and c) acute hypoxia caused by blocking the blood flow by means of vasodilatative drugs, tourniquet and embolization or endovascular catheter ballons. Eur. J. Oncol., 8 (1), 17-20, 2003

***Key words*: hypoxia, bioreductive perfusion, anticancer chemotherapy**

Riassunto

L'ipossia tumorale è considerata una limitazione sia per la radioterapia che per la chemioterapia dei tumori solidi. D'altra parte l'ipossia rappresenta anche un interessante obiettivo terapeutico, poiché è presente solamente nei tumori solidi. Le cellule ipossiche possono essere proposte per la terapia con profarmaci non tossici, attivati dall'ipossia. Concettualmente in questi farmaci le unità *trigger* sono attivate selettivamente nelle cellule ipossiche per liberare o attivare un "effettore" tossico, capace di uccidere le circostanti cellule tumorali ossigenate. Utili *trigger* comprendono chinoni, composti nitroaromatici, ossidi di azoto e metalli di transizione. Attualmente la tirapazamina (TPZ), un ossido di azoto, viene usata in studi clinici di fase III. Il tessuto dei tumori solidi è scarsamente perfuso rispetto ai tessuti normali. I motivi comprendono una vascolarizzazione tumorale assai limitata, poco strutturata ed inefficiente, ed alte pressioni interstiziali. Questo comporta, in molti tumori solidi umani, una disponibilità variabile di ossigeno, di altre sostanze nutritive e di farmaci, con conseguenti aree ipossiche (pressione parziale di ossigeno <5-10 mmHg). Tale ipossia può essere classificata in tre grandi gruppi: a) ipossia cronica o da diffusione, che rende le cellule, assai lontane dai più vicini capillari, ipossiche per lunghi periodi; b) ipossia transitoria o da perfusione, dovuta ad un'occlusione temporanea dei vasi, che produce aree ipossiche per periodi più brevi; e c) ipossia acuta, provocata da un blocco del flusso ematico dovuto a farmaci vasodilatatori, *tourniquet*, embolizzazioni o cateteri occludenti. Eur. J. Oncol., 8 (1), 17-20, 2003

***Parole chiave:* ipossia, perfusione bioriduttiva, chemioterapia antineoplastica**

Pervenuto/Received 26.8.2002 - Accettato/Accepted 20.11.2002
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Introduction

Cancer physiology can be a new significant target for therapy. Nonsurgical approaches to cancer treatment, primarily radiation therapy and chemotherapy, are almost exclusively based on agents that kill cells. The main problem with these current treatments, however, is that they do not have specificity for cancer cells. In the case of anticancer drugs, it is primarily the rapid proliferation of many of the cancer cells that makes them more sensitive to cell killing than their normal cellular counterparts, for radiation therapy, a degree of specificity is achieved by localizing the radiation to the tumour and its immediate surrounding normal tissue. However, both modalities are limited by their toxic effects on normal cells. In the case of radiotherapy, normal tissue surrounding the tumour limits the radiation dose, whereas for anticancer drugs, it is usually the killing of rapidly dividing normal cells, such as those in the bone marrow, epithelial cells lining the gastrointestinal tract and hair follicles, that limits the dose that can be given.

To achieve greater efficacy some scientists are attempting to stress differences between normal and malignant cells at the cellular and biomolecular level.

However, there is a second critical difference between normal and malignant tissues that has the potential for exploitation to produce a more specific anticancer therapy. The physiology of solid tumours at the microenvironmental level is sufficiently different from that of the normal tissues from which they arise to provide a unique and selective target for cancer treatment. Up to now, targeting tumour physiology for anticancer therapy has received much less attention based on the cellular and molecular differences between trasformed and normal cells.

The problem of tumour hypoxia in therapy

Tumour hypoxia is a very important factor in oncology, since it contributes to tumour progression by the activation of genes associated with their development, including those promoting angiogenesis. Moreover it has profound effects on therapy: oxygen helps to stabilise radiation damage in DNA, while hypoxic cells show considerable (about four-fold) resistance to radiotherapy; this is considered the major cause for the failure of radiotherapy in some tumours. Attempts to overcome this effect include the use of oxygen-mimetic "radiosensiters" and multifractional radiotherapy to allow re-oxygenation of tumour tissue, raising oxygen intake to increase overall concentrations in tissues. Radiosensiters are drugs designed to act similarly to oxygen in fixing radiation damage in DNA, but they are less rapidly metabolised, and are therefore more widely distributed in tumour tissues. There are also good reasons why, and considerable evidence to show how, hypoxic cells in tumours limit the efficacy of anticancer drugs. Also, such cells are usually non-cycling, owing to the lack of oxygen and other nutrients, so they are more resistant to the large class of antiproliferative drugs that preferentially attack cycling cells. More generally, hypoxic, and especially chronically hypoxic cells are usually also the most remote from blood vessels, making them difficult to reach with high molecular-weight drugs or drugs that bind tightly to cell components.

The pioneering work of Gray *et al*[1] demonstrated that the sensitivity to radiation damage of cells and tissues depends on the presence of oxygen at the time of irradiation. The histological studies on human lung adenocarcinomas by Thomlinson and Gray[2] provided an explanation of the mechanism by which cells could become hypoxic in tumours. They postulated that, because of their unrestrained growth, tumour cells would be forced away from vessels, beyond the effective diffusion distance of oxygen in respiring tissue, thereby becoming hypoxic and eventually necrotic. Given typical values for intracapillary oxygen tensions and oxygen consumption rates, the oxygen diffusion distance would be approximately 150 μm.

There are two important further consequences of reducing oxygen concentration: (a) the fraction of proliferating cells and/or the rate of cell proliferation decreases as a function of distance from the vascular supply, a phenomenon that is largely the result of decreasing oxygen levels[3-5]. An important consequence of this hypoxia-induced inhibition of proliferation is that, because most anticancer drugs are primarily effective against rapidly dividing cells, their effectiveness would be expected to fall off as a function of distance from blood vessels. This has been shown experimentally[1-7]; and (b) since hypoxic cells are the ones most distant from blood vessels, they will be exposed to lower concentrations of drug than those adjacent to blood vessels, primarily as a result of the metabolism of such agents through successive cellular layers. The consequent reduction of cell kill by anticancer treatment is a function of the distance from tumour blood vessels. Hypoxia is a common feature of both human and animal tumours. The vast majority of human solid tumours have median pO_2 levels lower than their normal tissue of origin. In animal tumours, it can be shown that these hypoxic cells are also viable and contribute to the resistance of trasplanted tumours both to radiation and to some anticancer drugs. In human tumours, there is direct evidence, from measurements of oxygen levels, that hypoxia contributes to resistance to radiotherapy. Similar studies have not been performed with chemotherapy, although the evidence of a strong correlation between the response of head and neck cancers to chemotherapy and radiotherapy implicates hypoxia as a cause of drug resistance.

Hypoxia in solid tumours, however, has an important consequence in addition to conferring a direct resistance to radiation and chemotherapy[5-7]. Graeber *et al*[7] showed recently that low oxygen levels caused apoptosis in minimally transformed mouse embryo fibroblasts and that this apoptosis depended to a large extent on wild-type p53 genotype. They further showed, using these same cells growing as solid tumours in immune-deprived mice, that apoptosis co-localized with hypoxic regions in tumours derived from p53 wild-type mice. In tumours derived from p53 -/- cells, there was much less apoptosis and no co-localization with tumour hypoxia. These findings provide evidence that hypoxia, by selecting for mutant p53, might predispose tumours to a more malignant phenotype.

Clinical data support this conclusion. Studies on both soft tissue sarcomas and on carcinomas of the cervix have shown that hypoxic tumours are more likely to be metastatic.

The model of hypoxic cells occurring at the diffusion distance of oxygen is the classic model of tumour hypoxia generally attributed to Thomlinson and Gray[2]. However, others have proposed that tumour hypoxia can occur in a second way, by temporary obstruction or cessation of tumour blood flow, the so-called acute hypoxia model. Definitive evidence for this type of acute hypoxia arising from fluctuating blood flow, has come from elegant studies with transplanted tumours in mice using diffusion-

limited fluorescent dyes. Because fluctuating blood flow has also been demonstrated in human tumours, it is likely that this type of hypoxia is also present in human tumours. The consequences of acute hypoxia will be similar to those of the diffusion-limited hypoxia. Any cells surrounding a closed blood vessel will be resistant to radiation killing because of their lack of oxygen at the time of radiation and will be exposed to lower levels of anticancer drugs than those surrounding blood vessels with a normal flow. This would be expected to lead to differences in response to anticancer agents, as has been observed in experimental tumours.

The low oxygen levels in tumours can be probably turned from a disadvantage to an advantage in cancer treatment. Such a possibility was proposed 20 years ago by Lin[8], who reasoned that compounds based on the quinone structure of mitomycin C might be more active in hypoxic tumours. It was known that mitomycin C required metabolic reduction of the benzoquinone ring to produce the cytotoxic bifunctional alkylating agent. Lin reasoned that a lower oxidation reduction (redox) potential for tumour tissue, relative to most normal tissues, could increase reductive activation of these quinone derivatives in tumours. Although this was not the correct mechanism for the increased cytotoxicity of mitomycin C and certain analogues toward hypoxic cells (much lower levels of hypoxia are needed to change cellular redox potential), these studies were important in suggesting the potential of hypoxia-activated drugs and led to the concept of selectively killing the hypoxic cells in solid tumours.

It is important to note that specifically killing the hypoxic cells in tumours has greater therapeutic potential than oxygenating the cells or chemically sensitizing them to radiation or chemotherapy. Not only is the killing tumour specific (hypoxia is tumour specific), but the cells killed are the ones resistant to conventional therapy. The combined killing by two agents with complementary cytotoxicity is potentially much greater than that by two agents acting on the same cell population. The other major advantage of hypoxia-selective cytotoxins is their potential for providing enhancement to the killing of standard anticancer drugs.

Hypoxia-activated drugs

There are presently three different classes of hypoxia-specific drugs that are in use clinically or are being developed for clinical use. They are the quinone antibiotics, the nitroimidazoles, and the benzotriazine di-N-oxides. In the quinone class, the three principal agents of current clinical interest are mitomycin C, porfiromycin and E09. All are structurally similar and require reductive metabolism for activity. Each of them is converted by reductive metabolism to a bifunctional alkylating agent and probably produces its major cytotoxic activity through the formation of DNA interstrand cross-links.

Mitomycin C, considered to be the prototype bioreductive drug, was introduced into clinical use in 1958 and has demonstrated efficacy towards a number of different tumours, in combination with other selective drugs whose toxicity towards hypoxic cells is modest, with values for hypoxic cytotoxicity ratios (the ratio of drug concentration to produce equal cell kill for aerobic and hypoxic cells) of 1 (no preferential toxicity) to approximately 5. However, based on this activity, mitomycin C has been combined with radiotherapy in two randomized trials of head and neck cancer, the pooled results of which gave a statistically significant disease-free survival benefit[6-8]. Whether this promising finding is the result of preferential cytotoxicity of mitomycin C towards hypoxic cells or of cytotoxicity to both aerobic and hypoxic cells is, however, still an open debate.

The third drug in this series, E09, is a much more efficient substrate for DT-diaphorase than either mitomycin C or porfiromycin and shows high toxicity to both aerobic and hypoxic cells with high DT-diaphorase levels. Cells with low DT-diaphorase levels are much less susceptible to killing by E09 under aerobic conditions, but this drug shows a high, up to 50-fold, preferential toxicity toward hypoxic cells. However, the pharmacokynetics of this agent work against its clinical utility, and phase I clinical studies have shown little activity of this drug.

A second class of bioreductive agents is that of the nitroimidazoles, the first two of which, metronidazole and misonidazole, have been extensively tested as hypoxic radiosensitizing agents. Further drug development by Adams *et al*[9] produced a compound, RSU1069, which has been shown to be a highly efficient cytotoxic agent with activity both *in vitro* and *in vivo*. RSU1069 has an hypoxic cytotoxicity ratio of some 10-100 for different cell lines *in vitro*, and it, or its prodrug, RB6145, has shown excellent activity with mouse tumour models when combined with irradiation or agents that induce hypoxia. Unfortunately, however, clinical testing of RB6145 has been aborted due to irreversible cytotoxicity toward retinal cells.

TPZ is the first, and thus far, only representative of the third class of hypoxia-selective cytotoxins[6]. The mechanism for the preferential toxicity of TPZ towards hypoxic cells is the result of an enzymatic reduction that adds an electron to the TPZ molecule, forming a highly reactive radical. This radical is able to cause cell killing by producing DNA damage leading to chromosome aberrations. Moreover, DNA damage occurs only from TPZ metabolism within the nucleus. TPZ produces specific potentiation of cell kill by radiation and cisplatinum. Specifically, the synergistic cytotoxic interaction observed when TPZ and cisplatinum are given in sequence depends on the TPZ exposure being under hypoxic conditions. In fact, there is no interaction when TPZ is given under aerobic conditions. It has also been demonstrated that the cytotoxic activity of TPZ under hypoxia is independent of p53 gene status of tumour cells. This drug has 100-fold differential toxicity toward hypoxic *vs* aerobic cells.

Hypoxia, gene therapy and bioreductive perfusions

Based on experimental studies that evaluated the responsiveness of tumour cells under aerobic and hypoxic conditions, Teicher *et al*[10] classified chemotherapeutic agents into three groups: 1) preferentially toxic in aerobic conditions (bleomycin, procarbazine, streptonigril, actinomycin D, vincristine and melphalan); 2) preferentially toxic under hypoxic conditions (mitomycin C and adriamycin); 3) no major preferential toxicity to oxygenation (cisplatinum, 5-fluorouracil and methotrexate).

Experimental investigations also help clinicians to turn the physiological characteristics of solid tumours into a therapeutic advantage. Due to the poor vascular supply, solid tumours present hypoxic areas that have also low pH and low levels of glucose. Hypoxia is not only a major problem for radiation therapy, but also leads to resistance to most anticancer drugs. The induction of drug resistance can be partly explained by cell cycle block at the

G1 phase in hypoxic cells, as most anticancer drugs are primarily effective against rapidly dividing cells.

There are also other ways in which hypoxia might contribute to drug resistance. One is through the amplification of genes, such as dihydrofolate reductase, conferring various glucose-regulated proteins that appear to be responsible for resistance to doxorubicin, etoposide and camptothecin.

However, tumour hypoxia represents a unique target that could be exploited for selective cancer treatment. Since the observation that drugs like nitroimidazoles and mitomycin undergo bioreductive activation and are more toxic under hypoxic conditions, a lot of preclinical studies have been performed ranging from the chemistry of the reductive process of drug activation to *in vitro* and *in vivo* studies, in rodent and animal tumour cells. A detailed chemical understanding of the mechanism of action of a variety of bioreductive agents is now available. The enzymatic processes by which these drugs are activated and the cofactors involved in this activation are becoming well understood.

The newest direction for exploiting tumour physiology is aimed toward the evolving field of gene therapy. In this novel approach to anticancer therapy, genetic material is transferred into cells with the ultimate goal of selectively killing cancer cells and sparing normal cells. Recent studies have regarded the possibility of using the hypoxia-signalling pathway to selectively activate gene expression[11-12]. Hypoxia induces the expression of a number of genes, principally via the stabilization of members of the bHLH/PAS family of transcription factors that bind to a consensus DNA sequence, the hypoxia response element (HRE). Physiologically regulated expression vector systems, containing HRE sequences, are now under development, to target therapeutic gene expression to tumour cells characterized by low oxygen tension[11]. From a clinical point of view the combination of hyperthermia and hypoxia seems to add activity to intra-arterial chemotherapy[12]. At the same time the exposure of body regions, such as pelvis or limbs, to a locally high dose of bioreductive agent such as mytomicin C, in hypoxic conditions shows activity in refractory cancers[12-16].

Conclusions

The discovery, about 50 years ago, that hypoxic cells are resistant to X-rays led to the concept that cancers might be resistant to radiotherapy because of their poor oxygen supply and subsequent hypoxia. Now tumour hypoxia is seen as a mechanism of resistance to many antineoplastic drugs, as well as a predisposing factor toward increased malignancy and metastases. However tumour hypoxia is a unique target for cancer bioreductive therapy that could be exploited for therapeutic use[16]. A hypoxic cell is unable to have a stable pH; this increases the permeability of the cell membrane so that antineoplastic agents can easily move through the membrane improving the global concentration of the drug both inside and outside the cell. The hypoxic conditions can be induced naturally or by vascular occlusive catheters during locoregional perfusion in order to achieve, in the tumour environment, a major efficacy of drugs that are potentiated by low oxygen concentration. This mechanism is used for chemoembolization and hypoxic perfusion with the stop-flow technique[13-15].

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Eur. J. Oncol., vol. 8, n. 1, pp. 21-25, 2003

Colorectal cancer screening in the third millennium

Screening del cancro colorettale nel terzo millennio

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Summary

***Introduction*. In the year 2000 it is estimated that there were approximately 3 million new cases of digestive cancer globally, with 2.2 million deaths. The term "digestive cancers" includes several forms of cancer affecting the digestive organs; the most common of those is Colorectal Cancer (CRC). It is estimated that half a million people died from CRC in the year 2000. *Prevention of CRC*. Primary prevention of CRC may be achieved by observing a low-fat diet, rich in fruit and vegetables. Several ongoing studies are exploring the possibility and feasibility of chemoprevention, particularly with non-steroid anti-inflammatory drugs. Secondary prevention of CRC may be achieved using some screening tests; these tests may save lives by detecting colorectal cancer in its earliest, most curable stage, and by detecting polyps, which can be removed, preventing them from developing into cancer. Several tests are available: the choice of which test to employ in screening is determined by the resources available. Up to now, only faecal occult blood test (FOBT) and flexible sigmoidoscopy (FS) have been employed in screening programmes on an asymptomatic population, while only limited initial experiences are available with colonoscopy. *Discussion*. The screening model based on the use of FOBT in average risk subjects has proved to be "efficient" in terms of reducing mortality rates by 15% to 33%; it is applicable on large population groups and is able to provide satisfying responses in term of diagnosis of neoplastic lesions. The recent study on FS by Atkin in the UK shows that a high compliance can be obtained also by this screening modality. The lower incidence of CRC in subjects submitted to polypectomy confirms the importance of screening programmes able to identify these precursor lesions at an early phase. Eur. J. Oncol., 8 (1), 21-25, 2003**

***Key words*: colorectal cancer, screening, FOBT, sigmoidoscopy, colonoscopy**

Riassunto

***Introduzione*. A livello mondiale si stimano per il 2000 circa 3 milioni di nuovi casi di tumori digestivi, con 2,2 milioni di morti. La dizione "tumori digestivi" include le neoplasie che colpiscono l'apparato digerente; la più comune tra queste è il Cancro del Colon-Retto (CRC). Si valuta che nel 2000 500.000 persone siano morte a causa del CRC. *Prevenzione del CRC*. La prevenzione primaria del CRC può essere ottenuta seguendo una dieta povera in grassi, ricca in frutta e vegetali. Alcuni studi stanno valutando la possibilità e la fattibilità di una chemioprevenzione, soprattutto con farmaci antiinfiammatori non steroidei. La prevenzione secondaria può essere attuata utilizzando alcuni tests di screening; questi tests possono salvare la vita diagnosticando il CRC in uno stadio precoce, facilmente curabile, ed identificando i polipi, che possono essere così rimossi prima della loro trasformazione maligna. Molti tests sono disponibili: la scelta dipende dalle risorse disponibili. Fino ad ora solamente la ricerca del sangue occulto nelle feci (FOBT) e la sigmoidoscopia (FS) sono state utilizzate in programmi di screening su soggetti asintomatici, mentre solo iniziali esperienze sono disponibili con la colonscopia. *Discussione*. I programmi di screening basati sull'uso del FOBT in soggetti a medio rischio si sono dimostrati in grado di ridurre la mortalità del 15-33%, di essere applicabili su ampia scala e di fornire risposte soddisfacenti in termini di scoperta di lesioni neoplastiche. Il recente lavoro di Atkin basato sull'uso della FS nel Regno Unito mostra che un'alta adesione della popolazione allo studio può essere ottenuta con la FS. Infine la riduzione dell'incidenza del CRC in soggetti sottoposti a polipectomia conferma l'importanza dei programmi di screening, capaci di identificare queste lesioni in una fase precoce. Eur. J. Oncol., 8 (1), 21-25, 2003**

***Parole chiave:* cancro del colon-retto, screening, ricerca del sangue occulto, sigmoidoscopia, colonscopia**

Pervenuto/Received 5.6.2002 - Accettato/Accepted 18.11.2002
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Introduction

Digestive cancers account for the highest number of cancers each year worldwide. In the year 2000 there were approximately 3 million new cases of digestive cancer globally, with 2.2 million deaths.

The term "digestive cancer" includes several forms of cancer affecting the digestive organs, the most common of which is Colorectal Cancer (CRC). It is estimated that in the year 2000 half a million people died from colorectal cancer (Table 1)[1].

Globally, CRC is one of the most frequent causes of cancer death in the more developed countries (Table 2), whereas it is the fourth if we considered worldwide mortality. Men and women are about equally affected[1].

CRC is preventable and highly curable (90% survival rate in the early stages). Unfortunately, most men and women are unaware of the disease, and the benefits of screening to achieve an early diagnosis are not met, especially when symptoms become apparent.

In Europe, in 1996, there were 213,111 incident cases and 110,669 deaths due to CRC[2]. The trend in incidence from 1970 to 2006 (R. Capocaccia, A. Verdecchia: The EUROPREVAL project, preliminary data, personal communication) shows a steady increase in all the European countries, whereas in the USA there is a downward trend starting in 1985[3]. These differences may be partially explained by the diffusion of endoscopic procedures (colonoscopy) with the consequent removal of precursor lesions, namely adenomatous polyps. In fact, in a recent report by Lieberman *et al*, out of 17,732 average risk subjects invited for a screening colonoscopy, 36.6% had already performed a colonic examination in the previous 10 years[4]. In addition, a downward trend in CRC mortality was observed in the USA from 1974 [5], while in Europe mortality is stable from 1985 (The EUROPREVAL project).

The reduction in mortality may be achieved as the result of an early diagnosis and removal of adenomatous polyps.

In fact it has been demonstrated that the removal of adenomas significantly reduces the incidence, and therefore mortality, of CRC[6-8].

Table 1 - New cases and expected deaths due to digestive cancer worldwide in 2000

Site	New cases	Expected deaths
Colon-rectum	944,717	492,411
Stomach	876,341	646,567
Liver	564,336	548,554
Oesophagus	412,327	337,501
Pancreas	216,367	213,462
Total digestive cancers	3,014,088	2,238,495

Prevention of colorectal cancer

Primary prevention of CRC may be achieved by observing a low-fat diet, rich in fruit and vegetables. In general a low calory intake and regular physical exercise seem to be responsible for the protective effect (Table 3).

Ongoing research will help answer questions about the extent to which dietary changes can protect against colorectal cancer, but a good diet is essential to good health in general.

Several studies are exploring the possibility and feasibility of chemoprevention, in particular with non-steroid anti-inflammatory drugs[9].

Secondary prevention of CRC may be achieved by using screening tests; these tests may save lives by detecting colorectal cancer in its earliest, most curable stages, and by detecting polyps, which can be removed, preventing them from developing into cancer.

Several tests are available; the choice of which test to employ in screening is determined by the available resources. Guidelines, available in many countries, provide specific recommendations on when to start and how often these tests must be used.

Table 2 - Cancer mortality in more developed countries (all ages): estimate for 2000

	Males				Females		
Site	Deaths	Crude rate	ASR (W)[(a)]	Site	Deaths	Crude rate	ASR (W)[(a)]
Lung	430,043	74.43	50.15	Breast	189,203	31.01	18.61
Colon-rectum	152,178	26.34	17.38	Lung	151,159	24.77	13.14
Stomach	138,699	24.01	16.16	Colon-rectum	149,470	24.49	12.27
Prostate	128,185	22.19	13.70	Stomach	91,240	14.95	7.73
Liver	68,992	11.94	8.07	Pancreas	62,957	10.32	5.12
Pancreas	65,773	11.38	7.65	Ovary, etc.	59,113	9.69	5.54

[(a)] Age Standardized Rate (World Standard)

Table 3 - How individuals can reduce their risk of colorectal cancer

Increase intake of vegetables and fruit	Eat five servings of fruits and vegetables each day Replace snacks such as chocolate, biscuits and crisps with an apple, orange, or other fruit or vegetable
Reduce intake of calories	In particular animal fats; often replace beef, lamb and pork with fish and poultry
Increase physical activity	By activities of moderate intensity, such as brisk walking
Supplement vitamins	In particular folic acid
Long term hormonal replacement for women (?)	

Among the screening tests available, we may list:
– faecal occult blood test (FOBT),
– double contrast barium enema (DCBE),
– flexible sigmoidoscopy (FS), and
– colonoscopy (TC).

Up to now, only FOBT and FS have been employed in screening programmes on an asymptomatic population, whereas only limited initial experiences with colonoscopy are available. The actual or possible sensitivity and specificity of the previous screening tests is reported in Table 4.

Table 4 - Sensitivity and specificity of screening tests

	Sensitivity	Specificity
FOBT for polyps	10%	90%
FOBT for cancer	40%	
DCBE for polyps/cancer	70%	98%
FS for polyps/cancer (in examined segment)	90%	98%
TC for polyps/cancer	90-98%	100%

From Winawer *et al*[5] (modified)

FOBTs

The FOBTs are non invasive, acceptable by patients, of low cost, and some of them may be readily performed also in the decentralized structures of a health network.

The rationale of the FOBTs is based on the fact that cancer and larger polyps usually bleed.

The most widely employed FOBT is the one devised by Greegor in 1967[10], based on the capability of guaiac to detect haemoglobin and its derivatives in faecal samples. Other tests, like the ones based on ortho-toluidine or benzidine, have been discontinued because of their toxicity or excessive sensitivity.

The FOBT used in most population studies is the guaiac test known as Hemoccult II, based on two samples from each stool for three consecutive bowel movements. The samples are smeared directly by the subject and the completed test card is then delivered to the reference centre or doctor. A recent slightly modified test is the Hemoccult II SENSA, which allows a more clear-cut interpretation of positivity.

The FOBTs based on guaiac pose problems of false positive and false negative results related to diet. In fact, non-human haemoglobins from meat, as well as other dietary components with peroxidase activity (spinach, etc.), may give false positives and suggest the opportunity for dietary restrictions, whereas an excess of vitamin C may give false negatives. In fact, rare red meat, the main culprit of false positives, seems to play a minor rôle: only 0.7% of false positive results were found with non-rehydrated test when consumption of red meat was allowed[11, 12].

Several studies have dealt with this problem and in fact some dietary guidelines are advisable, possibly restricted to just one day before the test, as in some of the major randomized studies[13, 14]. The important problem of intermittent bleeding of early lesions is partially overcome by the sampling of three consecutive bowel movements, whereas the false negativity by peroxidase is minimized by a delay in the development of the test of at least three days[11].

In the attempt to increase sensitivity without a significant loss in specificity, some new FOBTs, based on immunological methods, are entering into clinical practice. The most commonly used is Hemeselect, developed by Saito *et al* in 1984[15]. The test is specific for human haemoglobin, has a high sensitivity and an acceptable specificity, but its cost is much higher than the guaiac test. This fact has led to the guideline of testing only one stool sample, or two, but this is in great conflict with the biological rationale of intermittent bleeding[16, 17]. In addition, the development of immunological tests is strictly a laboratory procedure and requires 12 different steps, with related increase in costs for laboratory equipment and manpower. In other words, the immunological tests entail a totally different approach and are not suitable for their development and interpretation unless by appropriately trained doctors or nurses.

Allison *et al* performed the three tests, Hemoccult II (HO), the immunological Hemeselect (HSel) and Hemoccult II SENSA (HOS), on a cohort of over 8,000 subjects and were able to confirm an increased sensitivity of HSel and HOS with respect to HO (HO 37.1% - HSel 68.8% - HOS 79.4%), with a specificity for CRC rather similar for the three tests (HO 97.7% – HSel 94.4% - HOS 86.7%)[18].

The available results of randomized controlled trials (RCT)[13, 19, 20] and not randomized population studies[21, 22] are all based on Hemoccult II as a screening test. A significant reduction in mortality for CRC has been demonstrated in all studies, ranging from 15 to 33%. The favourable shift in staging for the cancers detected and the removal of adenomas consequent to total colonoscopy and polypectomy, employed as a second level examination, were responsible for the decrease in mortality. In the Minnesota study by Mandel *et al*, where a long follow-up is available (18 years), a reduction in incidence was also observed. The Mandel study has peculiar features because the sensitivity of the test was enhanced by rehydration and, as a consequence, a high number of subjects were submitted to colonoscopy (36%). The greatest mortality reduction in their study was achieved with annual repetition of the test. In fact, for those who complied with all the periodic annual tests, the reduction in mortality (45%) was even more striking (S.J. Winawer, personal communication). Table 5 compares rehydrated and not rehydrated tests.

Table 5 - Comparison of rehydrated and unhydrated tests in the Minnesota study

	Rehydrated	Unhydrated
Positivity	9.8%	2.4%
Sensitivity	92.2%	80.8%
Specificity	90.4%	97.7%
Positive predictive value	2.2%	5.6%

Double Contrast Barium Enema (DCBE)

The DCBE is an invasive technique that uses a barium enema, which reveals filling defects, and a subsequent insufflation of air after most of the barium has been removed, allowing lesions in the mucosa to be outlined by the retained barium.

Patients usually begin preparation 24 hours before the procedure, with a low residue or liquid diet, followed by laxatives and enema. Besides, it is important to note that patients are exposed to 300 - 500 mrem of radiation during a barium enema examination,

compared with the dose of radiation for mammography that is about 300 mrem.

Results from the literature suggest that the sensitivity of DCBE is 50-80% for polyps < 1 cm, 70-90% for polyps > 1 cm and 55-85% for Dukes A and B cancers.

Thus, several studies suggest that the performance of DCBE is insufficient in detecting a substantial percentage of clinically relevant lesions[5, 31].

Flexible Sigmoidoscopy (FS)

As a screening method, sigmoidoscopy has three important advantages with respect to FOBT or DCBE: 1) it allows a direct visualization of the mucosa; 2) lesions can be sampled or removed; 3) it has a high sensitivity and specificity for polypoid lesions in the segment of bowel examined.

The distal bowel is usually prepared by giving a saline laxative enema 1 - 2 hours before the procedure. Patients are not sedated and approximately 10-15% of them experience a moderate discomfort during the procedure. The major complication of sigmoidoscopy is bowel perforation; data from large series of FS show a perforation rate of 1 to 2/10,000 examinations. Slightly higher complication rates occur when biopsy or polypectomy are performed.

The limit of FS is that it explores only a part of the colon; a third or more of patients with proximal adenomatous polyps or advanced neoplasia had no distal polyps. If these patients had undergone only FS, they would not have been identified as being at increased risk of CRC[30].

Total Colonoscopy (TC)

Colonoscopy is the only technique currently available that offers the potential both to find and remove premalignant lesions throughout the colon and rectum. FOBT detects only those polyps and cancers that bleed; FS allows examination only of the distal third of the large bowel and DCBE, although it can image the entire large bowel, does not allow biopsy or polypectomy and has an important percentage of false negatives.

TC requires preparation of the bowel using laxatives with or without enemas, or large volumes of an oral cathartic solution. Patients usually receive intravenous sedation.

Sensitivity of TC is 90-95% both for polyps and cancer, with a specificity reaching 100%. The cecum is reached in 80-95% of procedures. A retrospective study of 429 patients who had a preoperative colonoscopy found that the findings at TC correlated with the pathological specimen in 97% of cases[23].

The disadvantages are linked to the capability and experience of the physician: the procedure takes 15-20 minutes for an experienced endoscopist, but much more for beginners. In a screening study on asymptomatic population, the cecum was reached in 98.6% of cases[24].

Data from six prospective studies of colonoscopy indicate that it can be complicated by perforation (1/1,000), major haemorrhage (3/1,000), and respiratory depression due to sedation, arrhythmia, transient abdominal pain and nosocomial infection. Mortality rate is approximatively 1-3/10,000, but no data are available on the rate of complications of diagnostic TC versus therapeutic TC (polypectomy)[25-29].

On 3,196 TCs, Liebermann *et al* reported 10 serious complications (total rate 3/1,000; six had bleeding, one had myocardial ischemia and one had a stroke), without perforations or deaths due to the procedure[4].

In a recent paper, again by Lieberman *et al*, it is shown that colonoscopy, in a screening setting, found an additional 24% of advanced neoplastic lesions with respect to FS and FOBT combined[30]. Another recent study strengthens the value of TC in screening, being 36% of diagnosed adenomas of the flat and depressed type, most probably "missed lesions" at DCBE[31].

Atkin recently published interesting results of a large randomized population study[32]: the compliance to FS was very high (71%) and only 5% underwent TC as a second level examination. Dukes A cancers were 62%, but no data are yet available from a long-term follow-up and on the rate of missed lesions in the proximal colon.

Discussion

The screening model based on the use of the FOBT in average risk subjects has proved to be "efficient" in terms of reducing mortality rates by 15% to 33%; it is applicable on large population groups and is able to provide satisfying responses in term of diagnosis of neoplastic lesions.

The recent study on FS in the UK shows that a high compliance can be obtained also by this screening modality.

The lower incidence of colorectal cancer in subjects submitted to polypectomy confirms the importance of screening programmes able to identify these precursor lesions at an early phase.

The efficacy of a screening programme employing colonoscopy can today be evaluated in terms of reducing the incidence of colorectal cancer, as the result of the endoscopic removal of adenomatous polyps. As already stated, the systemic removal of these lesions has lowered the incidence of cancer in subjects included in the National Polyp Study[6], in the Telemark study[33] and in the Italian multicentric study[7].

It is still not clear which is the best strategy to adopt: the occult blood test, the rehydrated occult blood test, the occult blood test and the sigmoidoscopy, a colonoscopy every 10 years or once or twice in a lifetime at an age at risk.

Colonoscopy is a highly specific and sensitive method, but burdened by high costs that, at the present time, exclude its use as a first-level examination in a mass screening programme. Other than the problem of costs, colonoscopy is not easily accepted by healthy subjects, being invasive and requiring a specific bowel preparation.

An intermediate solution which might be proposed to detect neoplastic intestinal lesions at an early stage is to carry out an annual occult blood test from the age of 45 onwards, as this is a simple, rapid and low-cost test with a high "acceptability" rate. A TC should then be carried out, even in the event of a negative occult blood test and in the absence of symptoms, between the ages of 55 and 62, and could be repeated after the age of 70 in cases in which life expectancy is still high.

In the opinion of many experts, the time has now come to offer colorectal cancer screening to the general population by different methods, with the aim of reducing mortality from the "deadliest and most preventable disease".

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Eur. J. Oncol., vol. 8, n. 1, pp. 27-31, 2003

A brief review of multifocal primary malignancy and asbestos exposure

Breve resoconto sui tumori maligni primitivi multifocali dovuti all'esposizione ad asbesto

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Summary

Rates for the occurrence of multifocal primary malignancy in the general population and in subsets have been calculated and studied in the search for further clues as to the causation of cancer. Over and above the variations in the criteria employed by authors in defining the phenomenon, inconsistent levels of vigilance, as well as different practices with respect to the coding of secondary causes of death, have militated against too strong a reliance on the data. Reported rates for the occurrence of multifocal primary malignancy in the general population vary according to the data source, from 1.2% in a hospital's general autopsy register, to 13.5% in a cancer register. Asbestos has been accepted as a multicentric carcinogen acting on bronchus, pleura and peritoneum, and there is evidence for a causal association with cancers of the larynx and of the gastrointestinal tract as well as other systems. Despite it being claimed that the data available for the study of asbestos are the most extensive occupational health data available, they are inadequate for reliably determining the full carcinogenic burden of asbestos, and its distribution by systems. The long term epidemiological study of cancers in an asbestos-exposed population has been designed but remains to be conducted. Eur. J. Oncol., 8 (1), 27-31, 2003

Key words: **multifocal malignancy, asbestos**

Riassunto

Il tasso di incidenza delle neoplasie maligne primitive multifocali nella popolazione generale e in gruppi specifici è stato valutato e studiato al fine di trovare ulteriori elementi che indichino la causa del cancro. Oltre alle variazioni nei criteri utilizzati da diversi Autori nel definire il fenomeno, anche livelli disuguali di vigilanza e differenti metodi di codifica delle cause secondarie di morte hanno impedito di fare completo affidamento sui dati. I tassi riportati sull'insorgenza di neoplasie maligne primitive multifocali nella popolazione generale variano a seconda della fonte dei dati e vanno dall'1,2% in un registro generale delle autopsie di un ospedale, al 13,5% in un registro tumori. L'asbesto è stato riconosciuto un agente cancerogeno multifocale che agisce su bronchi, pleura e peritoneo, ed esiste evidenza di un'associazione causale con i tumori della laringe, del tratto gastrointestinale e di altri apparati. Nonostante si affermi che i dati disponibili sull'asbesto siano quelli più ampi in tema di malattie professionali, essi sono comunque inadeguati a definire in modo affidabile tutto il potenziale cancerogeno dell'asbesto, e la sua distribuzione nei vari apparati. Lo studio epidemiologico a lungo termine sui tumori in una popolazione esposta ad asbesto è stato progettato, ma resta ancora da attuare. Eur. J. Oncol., 8 (1), 27-31, 2003

Parole chiave: **neoplasie maligne multifocali, asbesto**

Introduction

Reports of *multifocal primary malignancies* (synonyms include *multiple primary malignancies* and *primary carcinoma multiplex*) in an individual or in classes of individuals, have been *" ...viewed by the medical profession with the same detached curiosity as the freaks exploited by P.T. Barnum were viewed by the laity"*[1]. Alternatively, they have exercised the minds of pathologists and of epidemiologists hoping that they might find more clues to the causation of cancer than by the study of single malignancies. The phenomenon is considered generally, and its relevance to the evaluation of the total cancer burden of asbestos exposure is reviewed.

Pervenuto/Received 10.9.2002 - Accettato/Accepted 5.11.2002
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Defining multifocal primary malignancy

US National Cancer Institute (NCI) authors defined cancers to be multiple primaries if each arose within the same person but did

not represent a recurrence or metastasis, whether they originated within one anatomical site or in two or more sites[2]. A single lesion of more than one histological type they deemed to be a single primary, which they coded to the highest cytology. A second lesion of the same histological type in the same site as the first cancer (except bladder) they considered a separate primary if diagnosed after 2 months, unless stated to be recurrent. Although the NCI criteria did not specify that the cancers should be derived from epithelium or mucosa, the tumours discussed were exclusively of epithelial or mucosal origin.

There is however a school that applies the term *multifocal primary malignancy* where two or more primary malignancies arising from epithelium or mucosa, have originated in the same organ or tissue, as for example in the colorectal mucosa or in the urothelium (Dr P. Trott, personal communication).

NCI noted that investigators have generally excluded from analysis persons with cancer B as a second primary cancer relative to cancer A, if B is found at the same time or shortly after A was diagnosed. Because the simultaneous occurrence of two or more cancers is consistent with the hypothesis of common risk factors, they chose to retain those multiple primary cancers. In the presence of two or more primaries, they designated as the index site that where the cancer had the worst clinical prognosis, the furthest extension, or the most virulent histological type.

Time sequences of tumours

The prefixes *synchronous* and *metachronous* have been employed in relation to the time interval between the recognition of successive tumours, though authors appear to discriminate between these phenomena arbitrarily. When two or more tumours are identified in the course of a clinical examination or during an autopsy, there can be little disputation about the appositeness of the term *synchronous*. Its antithesis *metachronous,* even when applied to tumours recognised sequentially, with long time intervals between the diagnoses of first and subsequent tumours, is less clear cut. The perceived interval will be contributed to by delays in the patient's appreciation of the various effects, and by delays inherent in the investigative processes, as well as the time scale of carcinogenesis.

Some reports of multifocal malignancies

Over the past 70 years, a substantial body of literature has grown up of observations of multifocal primary malignancies in individuals and in general and selected populations. Reports on multifocal malignancies have been published as anecdotes, analyses of hospital records, analyses of autopsy registers, and reviews of population, cancer and death registers.

Some anecdotal reports

Single case reports or short series may be dismissed as mere curiosities, though careful reading would show that although a rare event was being recorded, awareness of the significance of the phenomenon being described would have been critical for the patient's best interests.

For example, the finding of a diffuse well-differentiated papillary mesothelioma of the peritoneum while operating on a rectal carcinoma must be an extremely rare event[3]. However, had the peritoneal "seeds" observed at exploratory laparotomy been misinterpreted as metastases from the rectal carcinoma, instead of surgical resection with a high probability of cure, the patient would have merely been treated palliatively.

In another case, the patient underwent resection of a localised adenocarcinoma of the rectum with clinical improvement[4]. At operation naked eye appearance of the peritoneum was normal, but 8 months later malignant mesothelioma of the peritoneum was diagnosed and 4 months later the patient was dead. At the time of the apparently successful resection, the platelet count was reported as 647,000/mm^3: this had risen to 828,000/mm^3 by the time the mesothelioma was recognised. High platelet counts have been reported in patients with malignant peritoneal mesothelioma, and attributed to the thrombocytopoietic properties of secretions from malignant mesothelial cells. The initial appearance of normality of the peritoneum notwithstanding, the thrombocytosis suggested that the mesothelial cells had already undergone transformation, and that a mesothelioma was developing.

Autopsy register reports

In a review of a consecutive series of 3,771 patients in the post mortem register of The London Hospital, *Primary Carcinoma Multiplex* was reported in 1.2% of all cases[5].

A review of 2,000 sequential reports of autopsies carried out on persons dying of lung cancer in two Russian towns, identified primary multiple malignant tumours in 67 cases (3.35%)[6].

The computerised Japanese Pathological Society autopsy register recorded 32,859 cases in 1979, 1078 of whom had 2-5 malignancies (3.28% of all autopsies)[7].

Cancer register and clinical records

The clinical and pathological notes for all patients with histologically confirmed malignant neoplasms seen at the Mayo Clinic and affiliated hospitals from January 1944 to December 31st 1953 were analysed[1]. They cited an earlier study of patients operated on at the Mayo Clinic for malignant lesions as finding 4.5% to have had multiple primary lesions. Excluding multicentric epitheliomas confined to the skin, during the 10 years of this study they found proven multiple malignancies in 1,909 cases (5.1%) out of a total of 37,580. The number of patients with primary neoplasms of different tissues was found to be 1,049, representing 2.8% of the total studied. They found patients in all age groups, from infancy to senescence, to be vulnerable, and no specific type of malignant neoplasm, either common or rare, rendered any absolute immunity against the occurrence of another primary malignant tumour (the authors included such tumours as those of brain and spinal cord, as well as leukaemia, lymphosarcoma, Hodgkin's disease, multiple myeloma, Kaposi's sarcoma).

A series of patients admitted to a Swedish hospital for the treatment of carcinoma of the lip between 1910 and 1950, was studied, of whom 1,675 were followed to death, or if they survived, to 1960[8]. The follow-up period was restricted to 30 years (average 12 years) as the numbers thereafter were too small. Of the 1,675 patients, 226 (13.5%) had a new primary neoplasm elsewhere than on the lip: 62 of these had 82 malignant skin tumours and

164 (9.8%) had 171 malignant tumours of other organs (the authors identified and included: brain tumours, sarcomas, malignant lymphomas, leukaemias, polycythaemia vera).

Of 676 patients entered on a hospital tumour register since 1974, 34 (average age 72 years) showed more than one site of malignancy, and of these 28 (4.1%) had two primary tumours and 6 (0.9%) had three primary tumours[9]. Common tumours presenting frequently, carcinoma of the prostate was an important contributor to the multiple tumours of males.

Between 1958 and 1988, 869,425 persons were registered on the Swedish national population-based cancer register, in whom 933,900 primary tumours were reported[10]. A subset of 97 patients, all of whom had more than one malignancy, with a total of 209 tumours, were selected for study. Second malignancy was diagnosed 94 months after the first on average (range <1-334 months), and the third malignancy 44 months after the second (range 1-171 months). In 1988 approximately 11% of the tumours reported were in persons earlier registered with another primary malignancy.

The cases of 9,415 patients with prior squamous cell carcinomas of the respiratory or upper digestive tract or other cell types of lung carcinoma recorded in the Memorial Hospital Tumour Registry for the years 1949-62, included 518 cases (5.5%) where cancers subsequently developed at other sites[11]. Patients with index cancers of nasal cavity, paranasal sinuses and nasopharynx did not develop excess cancers. Of the excess cancers, 73% occurred in other upper digestive or respiratory sites, 20% in the skin, and 7% in other organs or tissues. Those with primary lip cancers were at greatest risk of developing skin and intraoral cancers.

A five year prospective study was conducted on 733 patients admitted with a single primary epidermoid carcinoma of the oral cavity, pharynx or larynx, diagnosed and included on the Memorial Hospital Register from 1965 to 1968[12]. The average annual incidence for second primary carcinomas of the respiratory and upper digestive systems was 18.2 per 1,000 in men and 15.4 per 1,000 in women. An association with tobacco and alcohol was found for the index cancer and for the second primary cancer.

Nine standard geographically wide-spread population-based registries, assembled by the National Cancer Institute, were studied for the occurrence of multiple primary cancers associated with diet[2]. The data set included 176,021 first primary tumours diagnosed in men, and 181,064 in women, from 1973 to 1981. The total number of patients who developed more than one tumour was not presented nor were rates, as the authors were concerned with studying the relative risks of developing a second diet related tumour (in men these were colon-rectum, prostate, and in women colon-rectum, breast and uterine body); 1,455 (0.83%) of registered men, and 2,389 (1.32%) women had paired diet-related tumours.

Multifocal primary tumours in asbestos workers

A series of patients with known asbestos exposure and a full range of asbestos-related non-malignant effects was reported, among whom 5 were identified, each of whom had 2 definite or probable primary malignant tumours[13]. Two patients each had a lung carcinoma and a colon carcinoma, and three had two distinct pulmonary carcinomas. The authors provide no information on the source of the patients in their series, their number, or the rate of multiple malignancies, but they asserted that the development of multiple primary tumours after asbestos exposure is not common.

Among the 246 cases reported in the first analysis of the UK Mesothelioma Register, 3 had additional primary malignancies (1.2%)[14].

2,500 consecutive autopsies conducted by two pathologists from 1953 to 1964 were reviewed[15]. All patients with asbestos bodies and pulmonary fibrosis were deemed to have asbestosis and their histopathology was reviewed, as well as the cases of diffuse mesothelioma. In addition a parallel study was conducted on 45 cases of mesothelioma diagnosed in a Pathology Institute, and the underlying causes were analysed in 307 consecutive deaths among asbestos insulation workers. No cases of multifocal primary malignancy were reported.

A study of Italian railway workers exposed to asbestos reported 199 cases of malignant mesotheliomas at various sites, and 275 with other malignant tumours[16]. No mention was made of multifocal malignancy.

Studies of asbestos workers in which the expected excesses of asbestos-associated causes of death were observed, including lung cancer and mesothelioma, and in which histological confirmation was sought, have been reported. One, that also found excesses of carcinoma of the larynx and of the gastrointestinal tract, made no mention of multifocal malignancy[17]. Follow up to death of 1074 retired asbestos workers also produced excesses of deaths due to lung cancer, mesotheliomas, stomach cancer, kidney cancer and cancer of the eye, but made no mention of multiple tumours[18].

The final analysis of mortality of Quebec's chrysotile miners and millers included 657 cases of lung cancer, 38 cases of mesothelioma and 1,205 of other malignancies (including excesses of gastric and laryngeal cancers)[19]. No multiple malignancies were noted, nor were any reported in the final Quebec analysis of lung cancer and dust exposure[20], which looked at 539 cases of lung cancer and some 1,800 referents.

Asbestos as a multifocal carcinogen

The first hurdle was for asbestos to be recognised as a carcinogen. Gloyne[21] was non-committal about the causal association between the cases of lung cancer and occupation that he identified among local asbestos factory workers, but from the aggregation of reports in the world literature by the early 1940s, German physicians[22] and an American expert[23], were so persuaded. Doll's report in 1955[24] left no grounds for serious doubt. Only 5 years later, publication of a series of mesothelial tumours associated with asbestos exposure[25], non-committal though its authors were, confirmed evidence that had accumulated since 1935 onwards for a causal association, which consisted of several published cases of asbestos workers diagnosed as dying of malignant mesotheliomas, and not a few cases sequestered in asbestos company records[26]. This indicated that asbestos as a carcinogen was able to act remotely from the bronchus to affect pleura and peritoneum.

Excess risks have been claimed for other cancers and contested. Thus, concerning *laryngeal cancer,* a group of experts under the aegis of the United Nations Environment Programme (UNEP), International Health Organization (ILO) and World Health

Organization (WHO) in an International Programme on Chemical Safety (IPCS) report[27], could maintain that a risk while plausible had not been formerly established. Nevertheless they cited another opinion that asbestos should be regarded as one of the causes of laryngeal cancer[28]. As for an excess *gastrointestinal cancer* risk of asbestos, the IPCS report considered that although an excess risk associated with asbestos exposure had been reported in 18 cohort studies, 12 other studies had been negative, so they could not confirm it. They also felt that *kidney, liver, pancreatic* and *ovarian* cancers had not been firmly established as being at a risk.

In another review of the epidemiological evidence, 11 studies of populations of workers who had been exposed to various types and concentrations of asbestos in a variety of occupations, and who had been followed for 20 years or more, were analysed for evidence of asbestos being a systemic carcinogen[29]. Observed - expected ratios for *non-pulmonary cancers* were calculated to be in the range 0.97-2.78, much as for *gastrointestinal cancer*. A dose response gradient was observed for *gastrointestinal* and for *non-pulmonary cancers,* either when asbestos doses had been measured or when lung cancer ratios were used as surrogates. The author considered that the full extent of multicentre cancer mortality associated with asbestos exposure merited confirmation by a prospective study. Such a comprehensive study, including immunological and host change studies as suggested by Goldsmith, had earlier been instituted in the UK[30]. With the cooperation of the industry and the Trade Unions, a longitudinal national asbestos worker study, designed to run for decades, was begun in 1970, to settle a number of outstanding questions whose answers were deemed important. Unfortunately it was not to be completed.

Problems in the evaluation of data on multifocal malignancies of asbestos workers

While it was once claimed that the lung cancer death rate world-wide for workers exposed to asbestos had been no worse than for the non-exposed[31], even the most ardent asbestos protagonist no longer holds with this and has not suggested that asbestos protected against carcinogenesis. Consequently, asbestos workers might be expected at least to experience the same rate of multifocal malignancy as in a general population. In practice, if the comparison were made with the general population and there were no increased risk for asbestos workers, one might nevertheless expect to observe a spurious increased rate of multifocal malignancy in any substantial population of asbestos workers, as for many years now in a number of countries awareness and in consequence vigilance will have been greater in their case. Considerations of Social Security benefits and Civil Claims for negligence, will have focussed clinical investigation, and will have biased the autopsy rate for asbestos workers and improved the standard of diagnosis, to increase the reporting of synchronous malignancies. Research workers nevertheless have suspected that death registrations understate the true attributable burden of asbestos-associated disease, and in attempts to remedy this shortfall, some have looked for *best evidence*, reviewing clinical notes, tissues and sections. The resulting data have overlooked the phenomenon of multifocal malignancy and hence have not been able to provide *best measure* of the total cancer burden of asbestos exposure.

Biological plausibility for the multifocal carcinogenicity of asbestos

The naïve model of asbestos fibre toxicokinetics has inhaled fibre that is deposited in the larger airways of the nose, throat and bronchus, promptly swept out, if not subsequently expectorated, then swallowed and discharged safely though the gastrointestinal tract. A model of the same degree of sophistication, has respirable fibres that have successfully penetrated the airways largely confined to the lung parenchyma, though some translocation may be presumed to account for the development of pleural mesothelioma. According to asbestos species, the fibre remains *in situ*, with or without a coat, or undergoes dissolution. A simple version of carcinogenesis that requires the fibre *per se* to be the agent, argues for it being unable to operate multicentrically as it cannot reach parts further from the lung parenchyma than the pleura (it is held as a self-evident truth that ingested fibre cannot penetrate the gut wall). Even if the process of asbestos carcinogenicity were simply a matter of the direct action of the fibre, there is evidence derived experimentally and from human study, that a proportion of ingested asbestos fibres promptly enters the body and undergoes haematogenous spread throughout. The variety of functional and organic effects of mineral fibres observed experimentally at sub-cellular, cellular and tissue levels, as well as systemically, include, disrupting mitosis, inducing biochemical changes associated with morphological transformation, inducing frank transformation, and leading to immunological effects, suggesting a highly sophisticated model for their carcinogenicity.

Conclusion

The question is not one of whether asbestos is a multifocal carcinogen, but rather of how extensive its effect, and as a consequence what is the true total cancer burden resulting from asbestos exposure? In the pursuit of synchronous multifocal malignancies, the best vigilance in recognition and diagnosis for the purposes of death and cancer registration and the punctilious completion of their entries, will be defeated if secondary causes fail to be coded. As for metachronous multifocal malignancies, the value of a national cancer register will depend on how long it has been in existence. The best measure of the total burden of asbestos-associated cancers, and how they are distributed by systems would have been provided by longitudinal studies of substantial populations for whom measures of exposure were available, but this constitutes another of the numerous lost opportunities in the saga of asbestos.

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Eur. J. Oncol., vol. 8, n. 1, pp. 33-38, 2003

The rôle of growth patterns, according to Kodama's classification, and lymph node status, as important prognostic factors in early gastric cancer: analysis of 412 cases

Il ruolo delle modalità di crescita, secondo la classificazione di Kodama, e dello stato linfonodale come importanti fattori prognostici nell'early gastric cancer: analisi di 412 casi

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Summary

Background. **During the 1970s, a special type of gastric cancer with favourable prognosis (Early Gastric Cancer = EGC) was identified by the Japanese Research Society for Gastric Cancer. EGC has been defined as a tumour which invades the mucosa and/or submucosa, regardless of the lymph node status. Using this definition, the authors identified an initial phase of tumour development, which could be treated both endoscopically and surgically.** ***Methods.*** **All tumours were classified according to the macroscopic and microscopic criteria proposed by the Japanese Society of Gastroenterological Endoscopy and Lauren, respectively. The infiltrative growth pattern was evaluated according to Kodama's classification. Only tumour related death was considered as an end-point of interest for the survival analysis.** ***Results.*** **Submucosal tumours (p = 0.008), Penetrating (PEN) A Kodama type disease (p = 0.0001) and lymph node metastases (p = 0.0002) were significant prognostic factors in the univariate analysis. Moreover, the bivariate analysis showed that the worst prognosis was for patients with submucosal invasion and nodal involvement, and node-positive and PEN A Kodama type cancer. PEN A type EGC represents a subgroup of tumours, with a diameter of less than 4 cm, which infiltrates the submucosa extensively, causing the complete destruction of the *muscularis mucosae*.** ***Conclusions.*** **In our series, PEN A type according to Kodama was an important prognostic factor (Hazard Ratio = HR 8.32; 95% Confidence Interval = CI 3.49-19.86).**

Pervenuto/Received 28.6.2002 - Accettato/Accepted 26.9.2002
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Riassunto

Introduzione**. Negli anni '70, la Società Giapponese di Gastroenterologia Endoscopica identificò un tipo particolare di carcinoma gastrico a prognosi favorevole (Early Gastric Cancer = EGC). L'EGC fu definito come un tumore che invade la mucosa e/o sottomucosa, indipendentemente dallo stato linfonodale, curabile radicalmente con trattamento chirurgico e/o endoscopico.** ***Metodi.*** **Nella nostra serie abbiamo utilizzato le classificazioni della Società Giapponese di Gastroenterologia Endoscopica, di Lauren e di Kodama, rispettivamente per le caratteristiche macroscopiche, istologiche e infiltrative della neoplasia. Nell'analisi di sopravvivenza abbiamo considerato solo i pazienti deceduti per malattia.** ***Risultati.*** **L'infiltrazione della sottomucosa (p = 0,008), il tipo PEN A di Kodama (p = 0,0001) e la presenza di metastasi linfonodali (p = 0,0002) sono risultati fattori prognostici significativi nell'analisi univariata. Inoltre, l'analisi bivariata ha mostrato come tumori infiltranti la sottomucosa con metastasi linfonodali e tumori di tipo PEN A secondo Kodama con metastasi linfonodali abbiano una prognosi significativamente peggiore. L'EGC di tipo PEN A rappresenta un sottogruppo di lesioni che infiltra la sottomucosa massivamente, con crescita espansiva, di diametro massimo inferiore ai cm 4.** ***Conclusioni.*** **Nella nostra serie il tipo secondo Kodama (PEN A) è risultato essere un fattore prognostico importante (Hazard Ratio = HR 8,32; 95% Confidence Interval = CI 3,49-19,86). Perciò riteniamo importante valutare l'infiltrazione della parete in tutti i casi di EGC, facendo particolare attenzione al pattern di crescita del tumore. Inoltre, la prognosi dei pazienti affetti da EGC risulta essere significativamente peggiore quando a tumori di tipo PEN A si associano metastasi linfonodali. Pertanto, suggeriamo un trattamento**

For this reason, we believe it is important to evaluate the infiltration into the wall in all cases of EGC, paying particular attention to the growth pattern of the neoplasm. Moreover, submucosal PEN A type tumours had a considerably worse prognosis, particularly when lymph node metastases coexisted. We suggest, therefore, a surgical treatment with at least a D2 lymphadenectomy be performed in all these cases, as they must be considered to be advanced lesions and no longer EGC. Eur. J. Oncol., 8 (1), 33-38, 2003

***Key words*: EGC, prognosis, treatment**

chirurgico con linfoadenectomia estesa (almeno D2) per tutti questi pazienti, i quali vanno considerati affetti da tumori aggressivi, non più precoci. Eur. J. Oncol., 8 (1), 33-38, 2003

***Parole chiave:* EGC, prognosi, trattamento**

Introduction

During the 1970s, a special type of gastric cancer with excellent prognosis (EGC) was identified by the Japanese Research Society for Gastric Cancer (JRSGC)[1, 2].

EGC has been defined as a tumour which invades the mucosa and/or submucosa, regardless of the lymph node status[3-5]. Using this definition, the authors identified an initial phase of tumour development which could be treated both endoscopically and surgically[6-10].

The number of cases of EGC has progressively increased due to the better knowledge of the problem and the consequent improvement and diffusion of the endoscopic techniques[11-13]. Over the last 10 years, about 30% of all gastric cancer patients who underwent surgical treatment in our hospital had EGC[14, 15] (fig. 1).

In Japan, there are considerably more cases of EGC, now about 50-60% of all gastric cancers[16]. This large number of EGCs is due both to the presence of an active mass screening programme which was introduced a number of years ago[17], and to the existence of different classification systems for gastrointestinal dysplasia and gastric carcinoma in Western and Eastern countries[18-23].

Better knowledge of EGC and the improvement and diffusion of endoscopy have permitted the identification of subgroups of patients affected by EGC with a worse prognosis. These cases always require an aggressive therapeutic approach with a subtotal or total gastrectomy together with an extended lymphadenectomy (D2)[7, 14, 24-28].

In particular, the experience gained by evaluating the 412 patients affected by EGC with an average follow-up period of 9 years, has demonstrated that there is a significantly worse survival probability in node-positive submucosal and node-positive PEN A type patients[14, 15].

All patients were recruited and treated in an Italian region where there is a high incidence of gastric cancer[29].

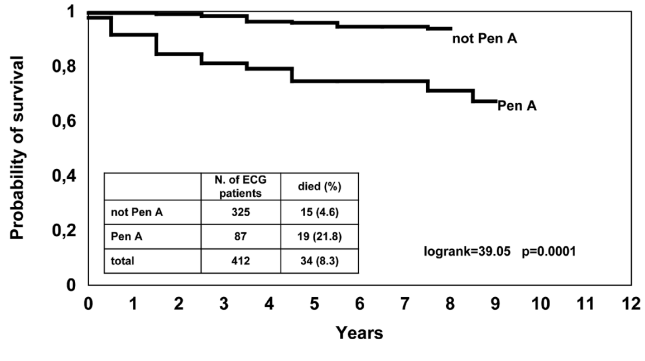

Fig. 1. Probability of survival, depending on growth pattern, according to Kodama's classification.

Materials and methods

From 1976 to 1997, 1955 patients affected with gastric cancer were treated surgically in the First Department of Surgery at the G.B. Morgagni-L. Pierantoni Hospital in Forlì (Italy). Among these, 493 were affected by EGC. The EGC/advanced cancer ratio was 25.2%. All the patients underwent a subtotal or total gastrectomy with a D2 lymphadenectomy.

The EGCs were classified according to the macroscopic and microscopic criteria proposed by the Japanese Society of Gastroenterological Endoscopy (JSGE)[2, 30] and Lauren[31], respectively. The JSGE divided the EGCs into polypoid (type I), elevated (type IIa), flat (type IIb), depressed (type IIc), and ulcerated (type III).

From the histological point of view, two major categories exist, designated intestinal and diffuse by Lauren. A third group includes unclassifiable or mixed tumoural lesions.

Kodama's classification was used to define the extent and type of penetration of the cancer[32]. According to this classification, the Super (superficial spreading) type is a tumour with a diameter of more than 4 cm either confined to the mucosa (Super M) or with a slight invasion of the submucosa (Super SM); the small mucosal type is a carcinoma with a diameter of less than 4 cm, with (Small mucosal SM) or without (Small mucosal M) slight submucosal invasion; the penetrating type (PEN) is a lesion with a diameter of less than 4 cm, with a widely invasion of the submucosa. This type is further divided into two subgroups, according to the way in which the *muscularis mucosae* is penetrated: PEN-A type, which invades the submucosa extensively and completely destroys the *muscularis mucosae* and PEN-B type, which grows infiltratively with fenestration of the *muscularis mucosae*.

The resected stomachs were opened along the greater curvature, pinned to a wooden plate and fixed in 10% buffered formalin. The tumours in the surrounding gastric wall were cut into several slices, mainly parallel to the lesser curvature, at intervals of 4-5 mm. Five μm thick sections, embedded in paraffin, were prepared from each slide for histologic examination.

All the microscopic sections, stained with haematoxylin-eosin, were examined by the same two pathologists, and the degree of

differentiation was classified according to the outline proposed by Watanabe *et al*[33].

Follow-up analysis was performed on the 412 patients examined. The average follow-up was 9 years (range 1-22). Survival analysis started the day in which EGC patients underwent surgical treatment. All the prognostic variables used in this analysis were measured at this time.

Only tumour-related death was considered as an end-point of interest for the survival analysis. Survival curves for EGC were calculated using the Kaplan-Meier method[34] and the difference between survival probabilities was analysed using the Log-rank test. The chi-square test was employed to define the association between the subgroups of pathological and clinical criteria examined. The HR evaluation, in univariate analysis, was obtained using Cox proportional model[35].

All p values were based on two-sided testing, and statistical analyses were carried out using SAS Statistical software[36].

Results

The median age of patients was 65 (range 30- 93) and the male/female ratio was 1.5:1; 245 were men (59.5%) and 167 women (40.5%). About 64% of EGCs were situated in the lower third of the stomach and almost all cases were monofocal (90.3%).

Intramucosal and submucosal infiltration were observed with similar frequency. As expected, the most frequent types were IIC EGC (54.3%) and SMM EGC (47.8%), according to macroscopic (JSGE) and Kodama's classifications. The most frequent histologic EGC was the intestinal type (77.7%) according to Lauren's classification. Lymph node metastases affected 55 patients (13.3%).

The lymph node status was significantly associated with the histologic type (p = 0.001), infiltration of the wall (p < 0.001), tumour size (p = 0.001), Kodama's type (p = 0.001) and macroscopic type (p = 0.02). In particular, the histologically diffused type, the macroscopically depressed type, ulcerated lesions (types IIC and III) and PEN A type, according to Kodama, gave lymph node metastases in more cases than the other subtypes (Table 1). Of the 412 patients, 284 (68.9%) are still alive and 128 (31.1%) died, of whom 34 (8.3%) as a result of the disease.

The survival probability of our series was 93% at 5 years and 89% at 10 years.

In a univariate analysis, patient age, gender and focality were insignificant prognostic factors. Conversely, a significantly lower survival probability was observed for patients with submucosal tumours (p = 0.008), PEN A type disease (p = 0.0001) and node positive cancers (p = 0.0002), than for the other anatomopathological subgroups (Table 2). In our series, in particular, the patients affected by PEN A type EGC had a death risk which was 8 times higher than those with non-PEN A type cancer (HR 8.32; 95% CI 3.49-19.86). This suggests that the biological behaviour of the neoplasm is closely linked to the growth pattern, according to Kodama's classification (fig. 1). Moreover, patients with the involvement of more than 3 lymph nodes (p = 0.0001) or of distant lymph nodes (p = 0.0001) had a considerably worse prognosis, reflecting a more advanced stage of the disease (figs. 2, 3).

Bivariate analyses were performed to evaluate the joint effect on survival of lymph node status and Kodama's subgroups (fig. 4), and of lymph node status and wall infiltration (fig. 5).

Table 1 - Distribution of lymph node metastases according to Kodama, Lauren and JSGE classifications

	N-		N+	
	No.	%	No.	%
Growth pattern (Kodama)				
Small MM	186	52.1	10	18.2
Small Msm	64	17.9	8	14.5
Super M	9	2.5	0	0
Super Msm	4	1.1	2	3.6
PEN A	55	15.4	32	58.1
PEN B	38	10.6	3	5.4
Histologic types (Lauren)				
Intestinal	291	81.5	29	52.7
Diffuse	66	18.5	26	47.3
Macroscopic types (JSGE)				
I	56	15.8	8	14.5
IIA	19	5.3	0	0
IIB	19	5.3	0	0
IIC	195	54.8	28	50.9
III	67	18.8	19	34.6

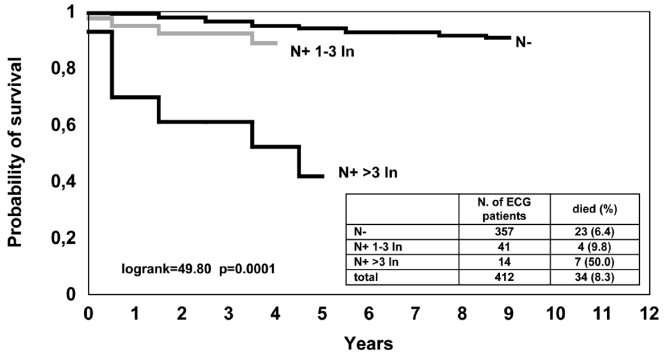

Fig. 2. Probability of survival, depending on number of lymph nodes involved: node-negative patients (n = 357); 1 to 3 node-positive patients (n = 41); > 3 node-positive patients (n = 14).

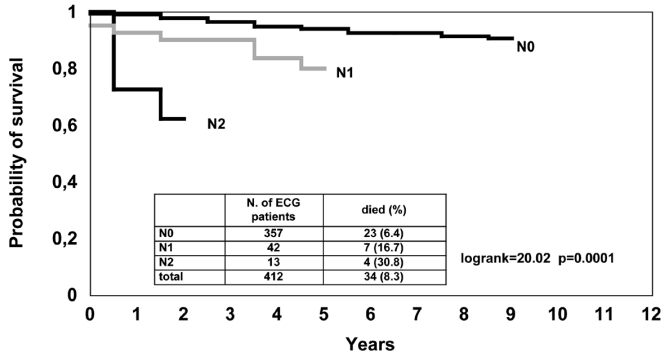

Fig. 3. Probability of survival, depending on the level of lymph nodes involved: node-negative patients (n = 357); I level node-positive patients (n = 42); II level node-positive patients (n = 13)

Table 2 - Univariate analysis: 5- and 10-year survival probability, the HRs and their relative 95% CI

	5-year	95% CI	10-year	95% CI	Log rank	p-value	HR (95% CI)
Depth							
Mucosal	96	93-99	93	89-97			1.00
Submucosal	88	83-93	85	80-91	7.05	0.008	2.60 (1.25-5.4)
Size							
< 2 cm	96	91-100	94	89-99			1.00
≥ 2 cm	88	82-95	86	78-94	4.85	0.088	2.43 (0.94-6.2)
Kodama							
Small MM	97	94-100	95	91-99			1.00
Small MSm	92	85-99	88	79-96			2.50 (0.88-7.13)
Super M	100		100				
Super Sm	100		100				
PEN A	74	64-85	67	53-81			8.32 (3.49-19.86)
PEN B	97	92-100	97	92-100	41.64 (5df)	0.0001	0.68 (0.08-5.51)
Nodes							
Negative	94	91-97	91	88-95			1.00
Positive	77	64-89	77	64-89	13.86	0.0002	3.57 (1.74-7.32)
No. nodes +							
0	94	91-97	91	88-95			1.00
1-3	89	78-99	89	78-99			1.62 (0.56-4.70)
> 3	42	13-71	42	13-71	49.80 (2df)	0.0001	11.42 (4.88-26.70)
N level							
N-	94	91-97	91	88-95			1.00
N1	80	67-94	80	67-94			2.79 (1.20-6.51)
N2	62	33-92	62	33-92	20.02 (2df)	0.0001	6.93 (2.39-20.08)

Discussion

The improvement and diffusion of endoscopic techniques and a greater knowledge of the problem have meant a significant increase in EGC cases over the last few years. In our province, EGC represents about 30% of all resected gastric cancers[14, 15]. In the 1970s, the most important prognostic factor was the depth of wall invasion. Subsequent clinical evidence, however, has consistently indicated nodal involvement as the most important prognostic parameter, so that only cancers without nodal invasion were considered as early neoplasms[8, 37]. By taking this into consideration, some authors demonstrated that patients affected with gastric cancer without lymph node metastases but with the invasion of *muscularis propria* behaved in a similar way to conventional EGC patients[8, 38, 39]. These findings would seem to classify all node-negative gastric cancers as Dukes A tumours, regardless of the depth of penetration[39]. Our previous studies showed that PEN A type growth pattern and lymph node status were two important prognostic factors in EGC patients[14, 15]. This study, performed on a series of 412 patients recruited in a region of Italy with a high incidence of gastric cancer, confirms such results. In particular, lymph node status seems to reduce patients' survival rate when

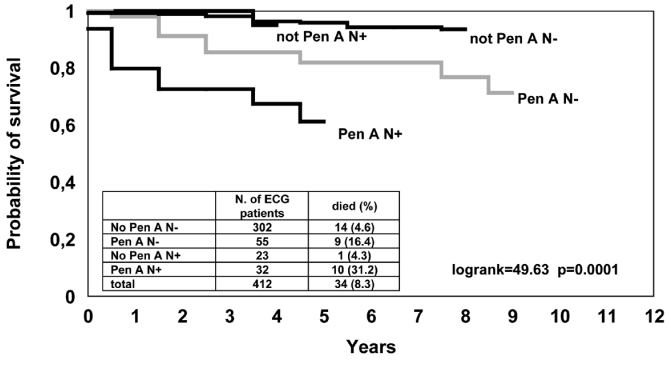

Fig. 4. Probability of survival, depending on wall and lymph node invasion: node-negative EGC limited to mucosa (n = 202); node-negative EGC invading submucosa (n = 155); node-positive EGC limited to mucosa (n = 7); node-positive EGC invading submucosa (n = 48)

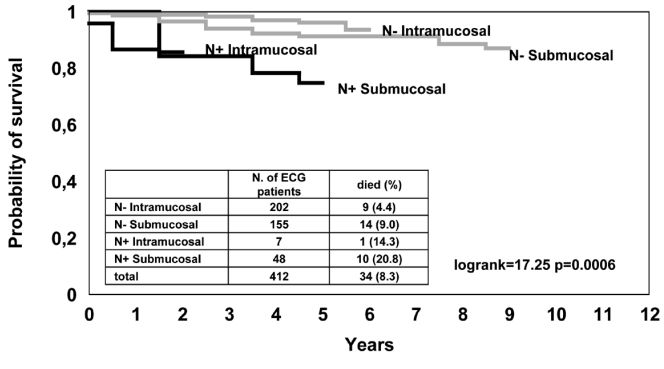

Fig. 5. Probability of survival, depending on the type of growth pattern and lymph node invasion: node-negative-non PEN A patients (n = 302); node-negative-PEN A patients (n = 55); node-positive-non PEN A patients (n = 23); node-positive-PEN A patients (n = 32)

more than 3 lymph nodes are involved or when there are lymph node metastases in the distal levels, according to the Japanese classification. Our results reinforce the rôle of PEN A type EGC, according to Kodama's criteria, as a significative prognostic factor, both in node-negative and node-positive EGC. Moreover, in our series, non PEN A types have a better prognosis than node-negative PEN A EGC, even when associated with the presence of lymph node metastases. The presence of nodal involvement and PEN A type growth pattern reduces the survival rate of our patients (61% at 5 years). Such tumours, although they are classified as EGC according to the JRSGC definition, have a significantly worse prognosis and, in our opinion, must be considered as being advanced lesions. Therefore, this knowledge suggests we must pay particular attention to these tumours, in order to perform the best surgical treatment, and this is worthy of consideration in subsequent studies, eventually to modify the definition of EGC.

Apart from our results, few reports have suggested modifying the definition of EGC, by identifying subgroups of patients with nodal metastases, characterized by worse prognosis[8, 38, 39]. According to these authors, wall infiltration was not as important as lymph node status for establishing the biological behaviour and prognosis of the tumour. Some of them, therefore, tried to introduce Dukes' classification for EGC[39]. Our conclusion gives a new contribution to the general knowledge of EGC, because of the identification of a new important prognostic factor, which is represented by Kodama's classification, which takes into consideration the extent and type of infiltration into the gastric wall.

In particular, submucosal PEN A type tumours had a significantly worse prognosis in our series and this fact was reinforced when lymph node metastases coexisted.

In our cases, however, PEN A type was a significative prognostic factor (HR 8.32; 95% CI 3.49-19.86). For this reason, we believe it is important to evaluate infiltration into the wall in all EGC cases, paying particular attention to the growth pattern of the neoplasm. These results are in agreement with our previous reports[14, 15], and have considered a larger number of cases.

In conclusion, we consider Dukes' classification to be well applied to gastric cancer as a simple and useful staging system[39] and wish to emphasise the important rôle of growth pattern, according to Kodama's classification, in identifying a subgroup of patients affected by a more aggressive type of EGC, with a clinical behaviour which is similar to that of an advanced lesion.

Moreover, in these cases, we suggest performing surgical treatment, which includes at least D2 extended lymphadenectomy, as several Japanese authors have previously proposed.

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Eur. J. Oncol., vol. 8, n. 1, pp. 39-41, 2003

I tumori del colon retto. La chirurgia delle localizzazioni multiple

Colorectal neoplasms. Surgery of multiple localization

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Riassunto

Al di fuori di condizioni precancerose ben definite come la rettocolite ulcerosa o la poliposi rettocolica familiare, l'osservazione di carcinomi multipli del grosso intestino è evento non frequente, ma nemmeno del tutto raro. Nella nostra esperienza degli ultimi 5 anni (1997-2001) consistente in 86 casi di carcinoma del colon-retto, i carcinomi multipli sono stati 5, pari al 5,8%; sono stati osservati un carcinoma sincrono (1,16%), uno sincrono-metacrono (1,16%) e 3 metacroni (3,48%). In entrambe le localizzazioni sincrone erano presenti polipi multipli disseminati, e tutte e tre le neoplasie metacrone sono insorte su polipi. In entrambi i casi di tumori sincroni le lesioni erano localizzate all'angolo colico dx ed al sigma; sono state eseguite due colectomie totali con ileorettostomia: uno dei pazienti, operato 17 mesi prima di resezione segmentaria in urgenza per un carcinoma stenosante della flessura sinistra, è andato perso al follow-up, l'altro è vivo dopo oltre 3 anni, apparentemente libero da malattia. In due delle localizzazioni metacrone, già operate rispettivamente di resezione del sigma e del trasverso, è stata effettuata una emicolectomia dx; un terzo caso, operato 20 anni prima di amputazione addomino-perineale, è stato sottoposto ad una resezione segmentaria degli ultimi 20 cm del colon ed a riconfezione della stomia per una neoplasia perianastomotica. Tutte e tre le pazienti, a distanza di 6-24 mesi dall'intervento, sono vive ed apparentemente libere da malattia. Inoltre è stata effettuata una bonifica preoperatoria in 8 casi. Un paziente è stato sottoposto a colonscopia intraoperatoria, 6 pazienti in follow-up sono stati sottoposti a bonifica di polipi insorti nel colon residuo; in un paziente di 50 anni, ripetutamente sottoposto a bonifica endoscopica per poliposi disseminata, l'insorgenza di un carcinoma del trasverso ha indotto ad eseguire la colectomia totale profilattica. Eur. J. Oncol., 8 (1), 39-41, 2003

***Parole chiave*: tumori colorettali, tumori multipli**

Summary

Apart from well-known precancerous conditions like ulcerative colitis or familial adenomatous polyposis, the observation of multiple carcinomas of the large intestine is not very frequent, even though not so rare. In our experience during the last 5 years of 86 cases of colorectal carcinoma, we found 5 cases (5.8%) of multiple carcinoma of the large intestine: 1 synchronous (1.16%), 1 synchronous-metachronous (1.16%), 3 metachronous (3.48%). In both synchronous cases multiple disseminated polyps were present and all three metachronous cases developed on polyps. Both the synchronous ones were localized in the sigmoid colon and at the hepatic flexure and the patients were submitted to total colectomy and ileo-rectal anastomosis: one of the patients had already been operated on as an emergency 17 months previously because of a stenotic carcinoma of the splenic flexure, but was lost at follow-up; the other patient is still alive and apparently disease-free after 3 years. Two of the metachronous cases, who had already undergone resection of the sigmoid and the transversum respectively, were submitted to a right colectomy, while the third case, who had undergone an abdomino-perineal amputation, 20 years previously due to new perianastomotic cancer was submitted to a partial resection of the last 20 cm of the colon, and the reconstruction of a new stoma. All three patients are alive and apparently disease-free at 6-24 months after the operation. Furthermore we have carried out preoperative endoscopic clearing of polyps in 8 patients, an intraoperative colonoscopy in 1 patient, and in 6 patients, during the endoscopic follow-up, we have found new polyps that have been resected; in a 50 year old patient, repeatedly submitted to endoscopic clearing for diffused polyposis, the onset of a carcinoma of the transversum made it necessary to carry out a prophylactic total colectomy. Eur. J. Oncol., 8 (1), 39-41, 2003

***Key words:* colorectal neoplasms, multiple neoplasms**

Pervenuto/Received 4.6.2002 - Accettato/Accepted 16.9.2002
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Al di fuori di condizioni precancerose ben definite, come la rettocolite ulcerosa o la poliposi rettocolica familiare, l'osservazione di carcinomi multipli del grosso intestino è un evento non frequente, anche se non del tutto raro.

Welch[1], in una revisione della letteratura, riporta un'incidenza media di carcinomi multipli del colon del 4%, con un range dallo 0,6 al 9,1%. Altrettanto riportano Fante *et al*[2] in una revisione di registri tumori.

Questi dati vengono, però, considerati sottostimati: Rodolico *et al*[3] sottolineano come non sempre sia possibile effettuare preoperatoriamente uno studio endoscopico completo del colon; Welch[1] afferma che molti cancri metacroni sfuggono per *drop out* o per morte dei pazienti per causa neoplastica o per altra causa prima di poter formulare la diagnosi di secondo tumore. In quest'ottica alcuni tumori "metacroni precoci", scoperti cioè entro 6 mesi - 1 anno dall'intervento, potrebbero essere meglio definiti come "sincroni misconosciuti"[4, 5].

Yamazaki *et al*[6] riportano un'incidenza di tumori metacroni del 10,6%; Arai *et al*[7], confrontando i dati di due casistiche, chirurgica ed autoptica, trovano un'incidenza di tumori multipli rispettivamente dell'8,6 e del 9,4%. Diversi Autori[8, 9] riportano come l'incidenza dei cancri metacroni aumenti con l'estendersi del follow-up.

Nella nostra casistica, che abbiamo voluto limitare agli ultimi 5 anni (1997-2001) su 86 casi di carcinoma del grosso intestino, i casi di carcinoma multiplo sono stati 5, pari al 5,8%: sono stati cioè osservati un carcinoma sincrono (1,16%), uno sincrono-metacrono (1,16%) e 3 metacroni (3,48%).

Lo sviluppo di neoplasie multiple, sincrone o metacrone, sarebbe espressione di una particolare tendenza di alcuni soggetti a rispondere agli stimoli oncogeni[3], potendosi definire anche dei gruppi con carcinoma colorettale ereditario (HNPCC o Sindrome di Lynch) in cui, oltre alla alta incidenza familiare vi è anche una maggiore tendenza alla plurifocalità del cancro colorettale[2, 10, 11].

Dal punto di vista clinico il fattore di rischio principale di sviluppare un secondo tumore, sia esso sincrono o metacrono, è costituito dalla presenza di adenomi come espressione di una instabilità rigenerativa della mucosa[6, 12, 13].

Welch[1] riporta, nei soggetti con tumori metacroni, la presenza di polipi nel 37% dei casi al primo intervento e nel 52% al secondo, mentre nei sincroni è del 65%.

Morson e Dawson[14] notano un 60% di adenomi associati al cancro d'esordio nei soggetti con tumori metacroni.

Secondo alcuni Autori[15,16] la presenza di polipi nel pezzo operatorio raddoppia il rischio di insorgenza di un secondo tumore.

Nei nostri casi, in entrambe le localizzazioni sincrone, erano presenti polipi multipli disseminati, e tutte e tre le neoplasie metacrone sono insorte su polipi.

Queste premesse definiscono come il trattamento delle localizzazioni multiple del cancro del colon non sia univoco, dovendosi identificare i principi di trattamento dei tumori sincroni e dei tumori metacroni, e le modalità di prevenzione dei tumori metacroni.

Per i tumori sincroni, ad un atteggiamento altamente demolitivo proposto da alcuni Autori[17-19], consistente nella colectomia totale di principio con ileo-rettostomia o nella proctocolectomia totale con ileostomia nei casi con coinvolgimento rettale, da Welch[1] in poi si è fatto strada un atteggiamento più eclettico, anche in considerazione del rischio di sequele e complicanze; se le neoplasie si trovano nella stessa area di drenaggio linfatico può essere considerata sufficiente una emicolectomia allargata, riservando ai casi di neoplasie distanti fra loro ed interessanti segmenti a diverso drenaggio linfatico la colectomia totale.

Nella nostra esperienza, in entrambi i casi di tumori sincroni, le due localizzazioni carcinomatose erano localizzate all'angolo colico dx ed al sigma; vi era inoltre, come già detto, la presenza di polipi, per cui sono state eseguite due colectomie totali con ileorettostomia: uno dei pazienti, ultraottantenne, che era stato operato 17 mesi prima di resezione segmentaria in urgenza, per un carcinoma stenosante della flessura sinistra, è andato successivamente perso al follow-up, l'altro, nonostante una positività per cellule neoplastiche nel liquido di lavaggio peritoneale, è vivo ad oltre 3 anni, apparentemente libero da malattia.

Analogamente l'insorgenza di un tumore metacrono non è obbligatoriamente un'indicazione ad una colectomia[1, 3].

Nella nostra casistica, nelle tre localizzazioni metacrone, in un primo caso, operato da noi un anno prima di resezione anteriore, è stato evidenziato al controllo endoscopico un polipo della flessura dx, che all'esame istologico ha mostrato presenza di un focus neoplastico; la polipectomia non è stata ritenuta sufficiente e si è quindi proceduto ad eseguire una emicolectomia dx. In un secondo caso, in una paziente operata altrove due anni prima di resezione del trasverso e giunta alla nostra osservazione per subocclusione intestinale da stenosi cicatriziale dell'anastomosi colocolica, è stata evidenziata alla colonscopia una neoplasia del cieco verosimilmente insorta su polipo; anche questa paziente è stata sottoposta ad emicolectomia dx. In un terzo caso, in una paziente operata da noi 20 anni prima di amputazione addomino-perineale, è insorta una neoplasia, a verosimile partenza da un polipo, in sede perianastomotica; la paziente, ultraottantenne, è stata sottoposta ad una resezione segmentaria degli ultimi 20 cm del colon ed a riconfezione della stomia. Tutte e tre le pazienti, a distanza di 6-24 mesi dall'intervento, sono vive ed apparentemente libere da malattia.

La prevenzione dei tumori metacroni trova il trattamento elettivo[6, 9] nella bonifica dei polipi pre- ed intraoperatoria, ricorrendo, se necessario, anche alla colonscopia intraoperatoria[12, 20], e nella sorveglianza con bonifica dei nuovi polipi. In alcuni casi selezionati, soggetti giovani con lunga aspettativa di vita, poliposi multicentrica o mucosa polipogena, e basso rischio operatorio, può, secondo alcuni Autori[21], essere proposta una colectomia totale profilattica.

Nella nostra esperienza la bonifica preoperatoria è stata effettuata in 8 casi, la colonscopia intraoperatoria in 1 caso, e 6 pazienti in follow-up sono stati sottoposti a bonifica di polipi insorti nel colon residuo; in un paziente di 50 anni, ripetutamente sottoposto a bonifica endoscopica per poliposi disseminata, l' insorgenza di un carcinoma del trasverso ha indotto ad eseguire la colectomia totale profilattica.

Possiamo concludere che, nel trattamento delle localizzazioni multiple del cancro colorettale, un trattamento ampiamente demolitivo vada riservato solo a casi selezionati; si impone però una stretta sorveglianza, soprattutto in pazienti che presentino fattori di rischio, per impedire l'insorgenza di tumori metacroni.

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Eur. J. Oncol., vol. 8, n. 1, pp. 43-46, 2003

Clinical benefit and objective response with gemcitabine as first-line therapy for patients with advanced pancreatic cancer

Beneficio clinico e risposta obiettiva con gemcitabina come prima linea terapeutica in pazienti con cancro del pancreas in stadio avanzato

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Summary

Background. **Advanced, surgically unresectable pancreatic cancer is an aggressive and lethal disease. Less than 10% of patients live one year after diagnosis and most of them suffer from increasingly severe pain, nausea, vomiting, anorexia, weight loss and weakness. Systemic treatment is used in widespread disease, but the impact of currently available chemotherapy is disappointing. In early studies with gemcitabine, patients experienced an improvement in disease-related symptoms. This trial assesses the efficacy of gemcitabine in patients with newly diagnosed advanced pancreatic cancer.** ***Patients and methods.*** **Twenty patients with advanced symptomatic pancreatic cancer were enrolled in this study. Gemcitabine was administered at the dose of 1,000 mg/m² per week for seven weeks, followed by a week of rest, and then for three weeks, followed by a week of rest for cycles of 4 weeks. The primary measure of efficacy was the response in terms of clinical benefit, defined by an association of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status and weight. Clinical benefit required a sustained (≥ 4 weeks) improvement in at least one parameter without any worsening in the others. Response rate, time to progression and survival were other measures of efficacy.** ***Results.*** **Clinical benefit was obtained in 6 (30%) of the enrolled patients. All patients were classified as positive in the pain category, with reduction in pain intensity and/or in analgesic consumption. The median duration of clinical benefit was 10 weeks. Partial response lasting 3 and 6 months was documented in only 2 patients (10%);**

Pervenuto/Received 3.9.2002 - Accettato/Accepted 19.12.2002
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Riassunto

Premessa. **Il carcinoma del pancreas in fase avanzata, non suscettibile di trattamento chirurgico, è una malattia aggressiva ad esito letale. Meno del 10% dei pazienti è vivo dopo un anno dalla diagnosi e la maggioranza di essi lamenta dolore severo ingravescente, nausea, vomito, anoressia, diminuzione di peso ed astenia. Il trattamento sistemico è utilizzato nella fase avanzata della malattia, ma l'impatto dei chemioterapici attualmente disponibili è deludente. In studi preliminari con la gemcitabina, i pazienti hanno ottenuto un miglioramento dei sintomi correlati alla malattia. Questo studio ha valutato l'efficacia della gemcitabina in pazienti con nuova diagnosi di carcinoma del pancreas in fase avanzata.** ***Pazienti e metodi.*** **Venti pazienti con carcinoma del pancreas sintomatico ed in fase avanzata sono stati arruolati in questo studio. La gemcitabina è stata somministrata alla dose di 1.000 mg/m² la settimana, per sette settimane di seguito seguite da una di riposo, e successivamente per 3 settimane di seguito con una di riposo con cicli di 4 settimane. La misura primaria di efficacia è stata la risposta in termini di beneficio clinico, definito come una serie composita di misurazioni del dolore (consumo di analgesici ed intensità del dolore), del performance status secondo Karnofsky e del peso. Il beneficio clinico richiedeva il miglioramento protratto, per 4 o più settimane, di almeno un parametro, in assenza di un peggioramento degli altri. Le risposte obiettive, il tempo alla progressione e la sopravvivenza erano le altre misure di efficacia.** ***Risultati.*** **Un beneficio clinico è stato osservato in 6 pazienti (30%). Tutti i pazienti sono stati classificati come positivi nella categoria del dolore, intesa come riduzione dello stesso e/o del consumo di analgesici. La durata mediana del beneficio clinico è stata di 10 settimane. Risposte parziali sono state documentate in soli 2 pazienti (10%), della durata di 3 e 6 mesi; inoltre, 4 pazienti (20%) hanno presentato una stazionarietà di malattia. Il tempo mediano alla progressione e la du-**

moreover 4 patients (20%) had stable disease. The median time to progression and median survival were 3 (range 1-8) and 6 months (range 2-20) respectively. All patients have since died; survival rate was 10.5% at 12 months; treatment was well tolerated. *Conclusions.* Gemcitabine has a marginal activity in the treatment of pancreatic cancer, with a limited improvement on parameters indicating a clinical benefit (pain intensity and analgesic consumption) and a mild toxicity profile. Eur. J. Oncol., 8 (1), 43-46, 2003

***Key words*: pancreatic cancer, gemcitabine, clinical benefit**

rata mediana della sopravvivenza sono stati rispettivamente di 3 (range 1-8) e 6 mesi (range 2-20).Tutti i pazienti sono deceduti; la sopravvivenza a 12 mesi è stata del 10,5%. Il trattamento è stato ben tollerato. *Conclusioni.* La gemcitabina possiede un'attività marginale nel trattamento del carcinoma del pancreas con un limitato miglioramento dei parametri utilizzati per definire il beneficio clinico (intensità del dolore e consumo di analgesici) ed un buon profilo di tossicità. Eur. J. Oncol., 8 (1), 43-46, 2003

***Parole chiave:* carcinoma del pancreas, gemcitabina, beneficio clinico**

Introduction

In Italy adenocarcinoma of the pancreas accounts for about 3-4% of cancer deaths[1]. Only a minority of patients are diagnosed with localized disease amenable to radical surgical resection; in the vast majority the disease is diagnosed in advanced or locally advanced stage beyond the scope of potentially curative treatment[2].

Advanced unresectable pancreatic cancer is an aggresive and lethal disease. Less than 10% of patients live one year after diagnosis, and most of them suffer from increasingly severe pain, nausea and vomiting, anorexia, weight loss and weakness[2].

Systemic treatment is used in widespread disease, but the impact of currently available chemotherapy is negligible. Fluorouracil is the most studied drug with a variety of doses and schedules of administration, but the response rate rarely exceeds 20% and no consistent effect on disease-related symptoms or survival has been demonstrated[3]. Biochemical modulation of 5-fluorouracil by leucovorin, N-(phosphonoacetyl)-L-aspartic acid (PALA), and interferon does not produce better results than 5-fluorouracil alone[4-8].

Other single agents or combination regimens offer no additional benefit over 5-fluorouracil as a single-agent; therefore, this drug has been traditionally considered one of the standard agents in the treatment of pancreatic cancer[9].

Recently, new drugs have been introduced in the chemotherapy of gastrointestinal tumours (irinotecan, oxaliplatin, capecitabine, gemcitabine).

Gemcitabine is a nucleoside analog that has multiple mechanisms of action, mainly via incorporation of gemcitabine di- and triphosphate into a growing strand of DNA, thereby inhibiting DNA synthesis. This drug also inhibits ribonucleotide reduction. It is self-potentiating, with an increasing formation of active metabolites and their lower elimination[10].

Gemcitabine has shown a wide spectrum of preclinical antitumour activity against a variety of solid tumours, including pancreatic cancer[11]. A very favourable toxicity profile, with a response rate of 10-15% and an advantage over 5-fluorouracil in terms of clinical benefit was demonstrated in phase II trials[12-15].

In a randomized trial of gemcitabine *vs* 5-fluorouracil, clinical benefit was 23.8% with gemcitabine and 4.8% with 5-fluorouracil, with a statistically significant difference ($p = 0.0025$) while the median survival was 5.65 and 4.41 months, respectively. Patients survival rates at 12 months were 18% and 2%, respectively. This trial was performed to assess clinical benefit, objective tumour response, progression-free and overall survival in patients with newly-diagnosed advanced pancreatic cancer[16].

Patients and methods

Patient selection

This study included 20 patients with histological or cytological diagnosis of pancreatic cancer, locally advanced or metastatic, not amenable to surgical curative resection. Previously treated patients were not eligible for enrollment in the study. Inclusion criteria were: a baseline Karnofsky performance status of 60, an estimated 12 weeks life expectancy, WBC count ≥3,500/μl, platelet count ≥100.000/μl, haemoglobin level ≥9.5 g/dl, adequate baseline hepatic function (i.e. a total bilirubin level ≤2.0 mg/dl, AST and ALT ≤three times the upper limit of normality, without liver involvement and up to five times in the case of liver involvement) and adequate renal function (serum creatinine ≤1.5 mg/dl).

Treatment

Gemcitabine hydrochloride was supplied as a lyophilized powder; it was diluted in normal saline solution and administrated intravenously over 30 minutes by an infusion pump. For the first cycle, patients received gemcitabine 1,000 mg/m^2 once weekly for up to 7 weeks, followed by a week of rest. Then gemcitabine was administered once weekly for 3 consecutive weeks followed by a weak of rest, for cycles of 4 weeks

Efficacy and safety evaluation

Clinical benefit. The first goal of this study was the evaluation of clinical benefit consisting in improvement of pain, functional impairment (primary measures), and weight loss (secondary measure). Patients were initially observed to assess a baseline measurement of pain. Pain intensity was then recorded daily (memorial pain assessment card = MPAC, and analgesic consumption diary); the other parameters and disease status were assessed weekly and every 4 weeks respectively.

Each patient was classified as positive, stable, or negative for each of the primary clinical benefit measures (Table 1). Positivity indicated a sustained (≥ 4 weeks) improvement over baseline. If the patient was stable on both primary measures of clinical benefit (pain and performance status), he or she was then classified positive or negative on the basis of the secondary measure (weight).

To achieve an overall rating of positive clinical benefit response, patients should have been positive in at least one parame-

ter (pain, Karnofsky performance status or weight) without being negative for any others.

Other measures of efficacy. Additional endpoints of our study were objective tumour response, time to progression and survival. A complete response was defined as disappearance of all evidence of cancer for 4 weeks or longer. A partial response was defined as a 50% reduction or more in the sum of the products of the perpendicular diameter of all lesions for 4 weeks or longer without any evidence of new lesions or progression of any lesion. No change was defined as less than a 50% reduction or less than a 25% increase in the sum of the products of the perpendicular diameters of all lesions without any evidence of new lesions. Progressive disease was defined as a more than 25% increase in one or more lesions or the appearance of any new lesion.

Time to progression was defined as the time between the administration of the first dose of the drug studied and the time of detection of progressive disease or interruption of therapy, whichever happened earlier. Survival was estimated as the time from the date of first treatment to death.

The characteristics of the 20 enrolled patients are summarized in Table 2. Four (20%) of them had locally advanced and unresectable disease and 16 (80%) had metastatic disease. Baseline Karnofsky performance status, pain intensity score and analgesic requirement were reported in the same table.

Table 1 - Classification for clinical benefit measures

Primary measures
Pain
Pain intensity (measured daily on the MPAC 0-100 visual analog scale)
1. Positive: an improvement of ≥50% from baseline sustained for ≥4 weeks, assuming a minimum pain score ≥20
2. Negative: any worsening from baseline, sustained for 4 weeks
3. Stable: any other result

Analgesic consumption (measured weekly in morphine-equivalent milligrams)
1. Positive: a decrease of ≥50% from baseline, sustained for ≥4 weeks, assuming a minimum analgesic consumption ≥10
2. Negative: any worsening from baseline, sustained for 4 weeks
3. Stable: any other result

Karnofsky performance status (measured weekly)
1. Positive: an improvement of ≥20 points from baseline, sustained for ≥4 weeks, for patients with a performance status of 60 or 70
2. Negative: any worsening of ≥20 points from baseline, sustained for ≥4 weeks
3. Stable: any other result

Secondary measure (measured weekly)
Weight
1. Positive: a weight gain (excluding third space fluid) of ≥7% from baseline, sustained for ≥4 weeks
2. Non positive: any other result

From Burris *et al*[16] (modified)

Results

Clinical benefit

A clinical benefit was obtained in 6 (30%) of the enrolled patients with a median duration of 10 weeks. All were classified as positive in the pain category (i.e., pain intensity and/or analgesic use reduction), whereas an improvement of ≥20 points from baseline 60 or 70 Karnofsky performance status or a weight gain of ≥7%, both sustained for ≥4 weeks, were not observed.

Other measures of efficacy

No patient achieved a complete response. Partial response was documented in only two patients (10%), lasting 3 and 6 months; moreover 4 patients (20%) had stable disease. The median time to progression and median survival were, respectively, 3 (range 1-8) and 6 months (range 2-20).

All patients have since died; survival rate was 10.5% at 12 months.

Five of the six patients who obtained clinical benefit did not achieve an objective response.

Toxicity

All patients were evaluated for toxicity. Ten patients (50%) showed leukopenia, only one with grade 4; in 4 patients (20%) grade 1 and 2 thrombocytopenia occurred; two patients (10%) experienced WHO grade 2 anaemia.

Nonhaematologic toxicity was generally mild; no WHO grade 3 or 4 toxicities were reported. Four patients (20%) had grade 1 or 2 nausea and vomiting; 15% of the patients showed grade 1 or 2 fever.

Table 2 - Patient characteristics

No. of patients	20
Median age (range)	71 (51-78)
Male / Female	8/12
Baseline Karnofsky performance status:	
60	4 (20%)
70	7 (35%)
80	7 (35%)
90	2 (10%)
Disease at presentation:	
locally advanced	4 (20%)
metastatic	16 (80%)
Sites of metastatic disease:	
liver	11
peritoneum	4
liver + peritoneum	1
Baseline pain intensity score:	
0-19	10 (50%)
20-29	5 (25%)
30-39	3 (15%)
40-49	1 (5%)
50-100	1 (5%)
Baseline analgesic requirement (morphine-equivalent mg):	
0-49	15 (75%)
50-100	5 (25%)

Discussion and conclusions

Attempts to develop effective systemic therapies for patients with locally advanced or metastatic pancreatic cancer have met with little success.

The current study considered the response in terms of clinical benefit as an endpoint of efficacy, using the criteria previously developed for the evaluation of gemcitabine in pancreatic cancer[16]. Clinical benefit, defined as a composite measure of pain, analgesic consumption, performance status and weight gain, has, recently, been included in the study of new therapies for this tumour and is recognized as a valid parameter for drug approval.

However, its clinical relevance should be estimated with caution; in fact, clinical benefit has not been validated[17]. This validation has represented an important and appropriate end-point for the evaluation of the treatment of advanced or metastatic pancreatic cancer, where palliation is a major goal.

Our study demonstrates that gemcitabine has a marginal activity, a limited positive improvement on a range of patient benefit parameters (such as pain intensity and analgesic consumption) and a mild toxicity profile.

Five of the six patients who obtained clinical benefit in this study did not achieve an objective tumour response. Such discrepancies between objective responses and clinical benefit have been observed in other clinical trials of gemcitabine[12, 14, 16, 18]. These data emphasize the difficulties in measuring pancreatic lesions and the possible lack of correlation between tumour regression and improvement of symptoms that can be measured, objectively, in clinical trials and give information on benefits of chemotherapy.

Future efforts will focus on evaluating gemcitabine in multimodality treatments and its association with new drugs.

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Eur. J. Oncol., vol. 8, n. 1, pp. 47-51, 2003

Fattori prognostici in pazienti affette da carcinoma mammario N_0. Contributo della nostra casistica

Prognostic factors in node-negative breast cancer patients. Our experience

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Riassunto

Obiettivo. **Lo studio si ripropone di valutare la rilevanza prognostica di Ki-67 in relazione ad altri parametri consolidati quali età, dimensioni, grading, ER, PgR, in un gruppo di donne affette da carcinoma della mammella con linfonodi negativi. La ricerca è finalizzata ad identificare marcatori sempre più affidabili che consentano una migliore stratificazione prognostica.** ***Pazienti e metodi.*** **147 pazienti affette da carcinoma mammario con linfonodi negativi, diagnosticato presso gli Spedali Civili di Brescia dal 1992 al 1995, sono state valutate retrospettivamente dopo almeno cinque anni di follow-up. L'età mediana è di 58 anni (range: 26-80), la dimensione mediana dei tumori è di 1,6 cm (range: 0,4-3,9). Il numero medio dei linfonodi prelevati dal cavo ascellare e valutati istologicamente è pari a 14 (range: 5-30).** ***Risultati.*** **Nell'analisi univariata delle variabili discrete, il grading (p = 0,0006), la negatività dello stato recettoriale per estrogeni (p = 0,0004) e per progesterone (p = 0,001) e la positività di Ki-67 (p = 0,0001) sono risultati importanti fattori prognostici nella determinazione del rischio di ripresa di malattia. La ploidia appare non significativa. Le variabili continue (età, dimensioni) non correlano significativamente con la prognosi. Si sottolinea che l'analisi multivariata con regressione logistica ha identificato Ki-67 come il parametro maggiormente predittivo del rischio di ripresa di malattia (RR = 4,13).** ***Conclusioni.*** **Ki-67 potrebbe apportare un rilevante contributo agli attuali modelli prognostici per il carcinoma della mammella con linfonodi negativi e nella nostra casistica si dimostra il parametro più significativo nell'analisi di regressione logistica. Eur. J. Oncol., 8 (1), 47-51, 2003**

Parole chiave**: linfonodi negativi, Ki-67, prognosi**

Summary

Aim. **The study evaluates the prognostic significance of Ki-67 with respect to other conventional markers such as age, tumour size, grading, ER and PgR status, in a group of patients with lymph node-negative breast cancer. This work aims at identifying ever more reliable markers, in order to allow a better prognostic stratification.** ***Patients and methods.*** **147 breast cancer patients without lymph node involvement, diagnosed at the Hospital "Spedali Civili" of Brescia from 1992 to 1995 were evaluated retrospectively, after 5 years of follow-up. The median age was 58 (range: 26-80); the median tumour size was 1.6 cm (range: 0.4-3.9). The average number of lymph nodes that were resected from the axillary cavity and histologically evaluated was 14 (range: 5-30).** ***Results.*** **In the univariate analysis of discrete variables, grading (p = 0.0006), negative ER status (p = 0.0004), negative PgR status (p = 0.001) and positive Ki-67 (p = 0.0001) have proven to be important prognostic factors in the determination of disease-free survival and overall survival. The ploidy does not appear to be statistically significant. The continuous variables (age, tumour size) are not significantly correlated with the prognosis. Multivariate analysis has shown Ki-67 to be the most predictive parameter of the risk of recurrence (RR = 4.13).** ***Conclusions.*** **Ki-67 could add an important contribution to the currently available prognostic models in node-negative breast cancer and, in our study, it has been shown to be the most significant marker in multivariate analysis. Eur. J. Oncol., 8 (1), 47-51, 2003**

Key words: **negative lymph nodes, Ki-67, prognosis**

Pervenuto/Received 30.7.2002 - Accettato/Accepted 7.11.2002
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Introduzione

Lo studio nasce dall'esigenza di analizzare il significato dei fattori prognostici nell'ambito di una categoria specifica di pazienti: le donne affette da carcinoma mammario con linfonodi negativi. In letteratura sono numerosi i lavori finalizzati ad individuare quei parametri che possano effettivamente prevedere il decorso clinico del tumore della mammella: la maggior parte di tali studi recluta pazienti con linfonodi positivi e negativi, indistintamente[1]. Tuttavia, a livello clinico, i fattori prognostici rivestono minor significato qualora vi sia un coinvolgimento linfonodale: viene infatti a decadere il loro ruolo nell'orientamento della strategia terapeutica, poiché in questo caso la scelta obbligata è verso l'impiego di una terapia adiuvante sistemica[2-4].

È invece il gruppo N_0 a beneficiare concretamente di uno studio delle variabili prognostiche, atte a stabilire i tumori maggiormente aggressivi e quindi candidati alla terapia medica postoperatoria. Dati recenti indicano infatti che il decorso in queste pazienti non è così omogeneo come si riteneva in passato: circa un terzo delle pazienti con linfonodi negativi ricade e muore entro 5 anni dalla diagnosi[5]. Questo dato è compatibile con le modalità di diffusione del tumore mammario, il quale, secondo l'ipotesi di Fisher, anche se di piccole dimensioni, ha la potenzialità di dare metastasi fin dall'esordio, potendo quindi essere considerato come malattia sistemica già al momento della diagnosi. Alla luce di questo, si comprende il motivo dell'elevata incidenza di ricaduta dopo sola terapia loco-regionale anche in presenza di linfonodi regionali negativi e si rende evidente la necessità di definire il rischio nell'ambito di questo sottogruppo di pazienti.

I parametri biologici, in particolare gli indicatori di proliferazione, dovrebbero consentire di individuare, all'interno di questa categoria ad apparente basso rischio, quei casi che hanno un tumore "biologicamente aggressivo", in modo da migliorare la definizione della storia naturale della singola neoplasia e di modulare su di essa la scelta terapeutica[5-9].

La definizione del rischio attraverso parametri prognostici classici (dimensione tumorale, grado istologico, età e stato recettoriale) ed aggiuntivi (Ki-67) mira dunque a risolvere i complessi problemi di gestione terapeutica legati al carcinoma mammario N_0.

Pazienti e metodi

Pazienti

In questo studio sono state reclutate 147 pazienti affette da carcinoma mammario ed esenti da coinvolgimento linfonodale, la cui diagnosi è avvenuta presso gli Spedali Civili di Brescia nel periodo intercorso tra il gennaio del 1992 ed il dicembre del 1995. L'analisi del significato prognostico dei principali parametri biologici è stata condotta attraverso uno studio retrospettivo, che si è avvalso di un follow-up di almeno cinque anni.

Il reclutamento di un numero di pazienti limitato, rispetto all'ampio lasso di tempo considerato, merita un'adeguata spiegazione. Innanzitutto si è scelto di considerare esclusivamente i casi N_0, poiché proprio per queste pazienti sono richiesti degli studi più approfonditi, riguardanti la determinazione del rischio e l'inquadramento prognostico. Le pazienti che presentano un coinvolgimento linfonodale (N+) sono *in ogni caso* sottoposte ad un regime chemioterapico adiuvante, successivo all'intervento chirurgico. Al contrario, le pazienti N_0 si devono avvalere di un'oculata stratificazione prognostica, affinché sia garantita un'adeguata terapia sistemica ai casi maggiormente a rischio. Ne è così conseguita una prima restrizione della casistica: dai 400 casi di carcinoma mammario maligno rilevati nell'archivio del II Servizio di Anatomia Patologica, in seguito alla consultazione dei referti compilati tra il 1992 e il 1995, è stato selezionato un sottogruppo di 147 pazienti prive di interessamento linfonodale, della cui documentazione disponiamo in modo completo. Infatti, i dati relativi alla terapia sistemica adiuvante eventualmente instaurata, all'andamento della malattia (comparsa di recidiva locale o a distanza) ed alla sopravvivenza globale al quinto anno di follow-up sono stati desunti dalle cartelle dell'archivio dell'Oncologia Medica degli Spedali Civili di Brescia.

Inoltre si è deciso di non far rientrare nello studio tutte quelle pazienti diagnosticate in anni precedenti al 1992 per due motivazioni: la prima è relativa alla disponibilità di una valutazione continuata di tutti i parametri biologici indagati. Ciò restringe l'osservazione ad anni relativamente più recenti, ossia al momento in cui le nuove metodiche immunoistochimiche e citofluorimetriche sono state introdotte di routine nell'analisi delle biopsie e dei pezzi operatori di carcinoma mammario. In secondo luogo, l'osservazione di un lasso di tempo più prossimo e limitato annulla un'importante variabile di confondimento, rappresentata dall'evolversi delle conoscenze sulla terapia medica e, conseguentemente, dal diverso trattamento postoperatorio. La terapia adiuvante rappresenta un fattore prognostico ampiamente riconosciuto: differenze nell'applicazione dei trattamenti medici potrebbero ripercuotersi sulla lettura del significato degli altri indici prognostici. Un'omogeneità nell'applicazione della terapia sistemica adiuvante è richiesta per migliorare l'attendibilità dello studio.

Infine, non ci si è avvalsi della documentazione relativa agli anni 1996-1999, nonostante fosse disponibile e completa, poiché ciò non avrebbe garantito uno studio con un adeguato follow-up, convenzionalmente ed ubiquitariamente fissato a cinque anni.

L'applicazione di criteri statistici maggiormente rigorosi, a discapito di una limitazione nel reclutamento delle pazienti, assicura un risultato sufficientemente attendibile dello studio.

Tutte le pazienti sono state stadiate secondo il sistema TNM suggerito dalla UICC. Per ogni paziente si è scelto di valutare una serie di parametri clinici e biologici.

Il diametro tumorale presenta un range compreso tra 0,4 e 4 cm, con valore mediano di 1,61 cm e deviazione standard di 0,76.

Lo stato linfonodale è indagato attraverso lo svuotamento chirurgico del cavo ascellare e l'analisi istologica dei linfonodi (come si è detto, in questo studio abbiamo valutato solo le pazienti N_0); l'assenza del coinvolgimento linfonodale è definita, nel nostro campione, in base al prelievo di un minimo di 5 fino ad un massimo di 30, con un valore medio di 14 linfonodi asportati e valutati istologicamente.

L'età è compresa tra 26 ed 80 anni (valore mediano = 57,1, deviazione standard = 11,2).

L'osservazione anatomo-patologica, condotta su sezioni colorate con ematossilina-eosina, relative al pezzo chirurgico, ha consentito lo studio del tipo istologico e del grading.

L'istotipo maggiormente rappresentato è quello duttale (76,2%), seguito dal lobulare (15%).

Il grado istologico, valutato secondo la classificazione di Bloom e Richardson modificata, mostra una netta prevalenza di

tumori G_2 (57,8%), mentre G_1 e G_3 sono rispettivamente il 15% ed il 27,2%.

L'utilizzo del materiale d'archivio incluso in paraffina, relativo ai 147 carcinomi, ha consentito la misurazione del livello di recettori per gli ormoni steroidei, dell'attività proliferativa e del contenuto di DNA.

Mediante gli anticorpi monoclonali diretti contro la proteina ER, è stato possibile definire lo stato dei recettori per estrogeni, convenzionalmente considerato positivo per valori superiori al 10%. Analogamente sono stati studiati i recettori per il progesterone, il cui cut-off è fissato dal II Servizio di Anatomia Patologica degli Spedali Civili di Brescia al 10%. I tumori *ER+* sono il 78,2%, mentre i *PgR+* sono di poco inferiori al 69%.

L'antigene nucleare di proliferazione Ki-67 è stato valutato mediante la tecnica immunoistochimica su sezioni in paraffina, avvalendosi dell'anticorpo monoclonale MIB1. Applicando un valore-soglia del 10%, i tumori Ki-67+ rappresentano il 37,4% della nostra casistica.

Infine, l'analisi con citometria a flusso dei campioni inclusi in paraffina ha consentito la determinazione del contenuto di DNA: i tumori sono stati suddivisi in diploidi (47,3%) ed aneuploidi (52,7%).

A cinque anni, 119 pazienti non presentano alcun segno di ripresa della malattia, mentre le restanti 28 sono recidivate localmente o a distanza. Di queste 28 pazienti, 15 sono decedute, come appare dall'analisi al quinto anno di follow-up.

Metodi

Questo studio si ripropone di saggiare il valore prognostico dei principali indici biologici nel carcinoma mammario, sia valutando la correlazione dei singoli fattori con la sopravvivenza a cinque anni, sia identificando l'indice prognostico più significativamente associato all'andamento della malattia, avvalendosi di un'analisi multiparametrica. Per l'analisi statistica delle variabili discrete è stato impiegato il *test* χ^2, mentre per le variabili continue e parametriche è stato applicato il *test t di Student*.

Per ciò che concerne l'analisi multivariata, sono state prese in considerazione tutte le variabili prognostiche in studio, al fine di verificare quale fosse il parametro maggiormente significativo nella stratificazione del rischio e nella definizione di un modello prognostico esauriente. In particolare, abbiamo applicato la tecnica di regressione logistica multipla. Tale analisi è caratterizzata dal vantaggio di attenuare le fluttuazioni casuali che si rendono particolarmente evidenti quando il numero dei soggetti nei sottogruppi studiati è piccolo[10]. Inoltre, poiché si tratta di un metodo efficiente per l'analisi degli esiti dicotomici, esso è particolarmente adatto per studi, sia di coorte sia retrospettivi, in cui tutti i soggetti abbiano periodi di follow-up della stessa durata. Per tali motivi, l'analisi di regressione logistica multipla si propone come il test statistico più adatto per l'osservazione multivariata del nostro campione di pazienti.

Risultati

Analisi univariata

Ciascun parametro prognostico discreto e continuo viene posto in correlazione con l'evento negativo (recidiva/decesso al quinto anno), al fine di valutare la contingenza tra il parametro osservato e la sopravvivenza. La probabilità ottenuta dall'applicazione dei test statistici di significatività dovrà avere un valore inferiore allo 0,1 ($p < 0,1$), affinché si possa affermare che l'associazione di tale parametro alla prognosi non sia imputabile ad una variazione casuale.

La variabile T non emerge dal nostro studio come parametro significativamente associato alla sopravvivenza ($p = 0,583$).

Il grado istologico è fortemente correlato con la sopravvivenza delle pazienti con carcinoma mammario N_0, configurandosi come una delle variabili prognostiche più importanti ($p = 0,0006$) (fig. 1). Abbiamo riscontrato una certa correlazione, anche se inferiore a quella del grading, tra la positività dello stato di ER e la sopravvivenza. Nonostante ER venga maggiormente considerato nella pianificazione della strategia terapeutica endocrina, la sua negatività si associa in modo significativo ($p = 0,0004$) al rischio di ripresa di malattia.

Per quanto concerne i recettori per il progesterone, anch'essi mostrano una correlazione significativa con la prognosi: la loro associazione è decisamente meno forte ($p = 0,001$) di quella evidenziata sia dallo stato dei recettori per estrogeni, sia dal grado istologico.

Il *test* χ^2 indica una strettissima correlazione tra la presenza di un indice di proliferazione basso, ossia un Ki-67 inferiore al cut-off del 10%, e la sopravvivenza delle pazienti reclutate ($p = 0,0001$) (fig. 2).

La ploidia non raggiunge un grado di significatività sufficiente a predire il comportamento della neoplasia ($p = 0,1084$).

Dal nostro studio, la variabile *età* non appare assolutamente correlata alla prognosi ($p = 0,5735$).

Analisi multivariata

Tutte le variabili analizzate vengono simultaneamente poste in correlazione con la prognosi, per verificare il contributo indipendente di ciascuna al rischio di ripresa di malattia. Il risultato dell'analisi multivariata del campione in esame è particolarmente in-

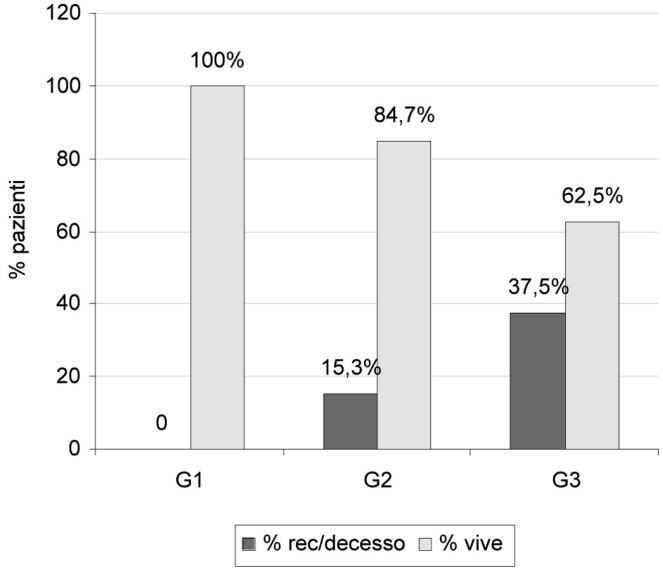

Fig. 1. Rappresentazione grafica dell'associazione tra grading e prognosi ($p = 0,0006$)

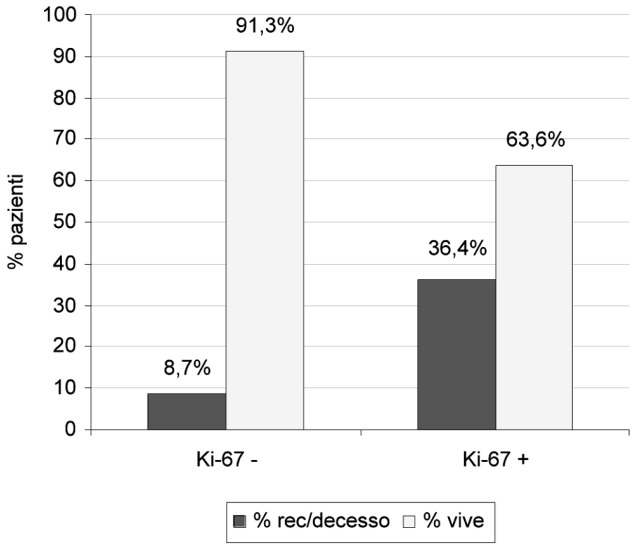

Fig. 2. Rappresentazione grafica dell'associazione tra Ki-67 (cut-off del 10%) e prognosi (p = 0,0001)

teressante: in pazienti affette da carcinoma mammario con linfonodi negativi, Ki-67 appare come la variabile maggiormente in grado di predire l'andamento della malattia, ridimensionando il ruolo non solo dei recettori ER e PgR, ma limitando in modo importante anche il valore del diametro tumorale. Il rischio relativo di recidiva legato alla variabile Ki-67 è pari a 4,13, con un buon coefficiente di dispersione (1,49-11,4).

In seguito all'osservazione della rilevanza prognostica del marcatore di proliferazione Ki-67 e grazie agli spunti forniti dalla letteratura riguardante le ipotesi del fallimento dell'ormonoterapia in un terzo delle pazienti con recettori positivi, si è ritenuto opportuno ampliare l'obiettivo di questo studio, verificando il possibile ruolo di Ki-67, non solo come fattore prognostico, ma anche predittivo della risposta alla terapia endocrina. Abbiamo selezionato dalla casistica di partenza tutte le pazienti ER e PgR positive, poiché ovvie candidate al trattamento endocrino postoperatorio. Abbiamo accertato, in base ai dati delle cartelle cliniche, che tali pazienti avessero effettivamente intrapreso la terapia adiuvante ormonale ed abbiamo escluso dallo studio le altre. Ai 64 casi così ottenuti si è applicato nuovamente il *test* χ^2, per saggiare la significatività dell'associazione tra un elevato indice di proliferazione e la mancata risposta all'ormonoterapia, nonostante la positività recettoriale. Il risultato dello studio non dimostra una correlazione tra Ki-67 e la capacità di predire la risposta alla terapia endocrina in pazienti con recettori positivi (p >0,1).

Conclusioni

I risultati ottenuti contraddicono, per certi aspetti, alcune delle più classiche osservazioni sul valore dei singoli fattori prognostici[11]. L'età della paziente e la dimensione tumorale non risultano significativamente correlate all'andamento della malattia; inoltre all'interno del sottogruppo di pazienti con linfonodi negativi sembrerebbe che il diametro della neoplasia non influisca sul rischio di ricaduta della paziente, né quando analizzato come variabile continua, né quando suddiviso per classi discrete. Il grading, al contrario, resta un parametro fortemente associato al decorso clinico del carcinoma mammario, come descritto dalla maggior parte della letteratura. I parametri predittivi della risposta alla terapia ormonale, ER e PgR, mostrano anche un chiaro significato prognostico. Il loro potere prognostico è comprensibile alla luce della loro stretta associazione e dipendenza da altri indici biologici, quali un basso grading ed un basso tasso di proliferazione cellulare.

Dallo studio emerge poi il ruolo francamente prognostico degli indici di proliferazione cellulare: l'analisi univariata identifica in Ki-67 il parametro più significativamente correlato al decorso clinico della malattia. Inoltre, l'osservazione multivariata conferma l'importanza di Ki-67 nel rilevare, all'interno del sottogruppo di pazienti N_0 con prognosi apparentemente buona, quelle neoplasie che presentano invece un atteggiamento più aggressivo, suggerendo che tale parametro possa migliorare l'attendibilità degli attuali criteri prognostici nel carcinoma della mammella.

L'entusiasmo per il ruolo emergente di Ki-67 ci ha portato a testare anche il suo significato predittivo nelle pazienti con recettori positivi che non rispondono però all'ormonoterapia. Nella nostra casistica, Ki-67 non appare correlato con la capacità di predire la riuscita della terapia endocrina: tra coloro che sono state sottoposte alla terapia con tamoxifene, poiché presentanti recettori positivi, il 57% dei casi con ripresa di malattia e il 79% delle pazienti con risposta all'ormonoterapia avevano un indice di proliferazione basso, testimoniando lo scarso valore delle indicazioni offerte da Ki-67 nella comprensione dei fallimenti del trattamento endocrino. Ki-67, dunque, pur essendo un importante fattore prognostico, non sembra aggiungere informazioni sulla predittività della risposta alla terapia endocrina rispetto a quelle fornite dalla positività dello stato recettoriale.

La problematica relativa al fallimento dell'endocrinoterapia in pazienti con recettori positivi presenta probabilmente molteplici sfaccettature: la presenza di un tumore particolarmente aggressivo, testimoniato ad esempio da un indice di proliferazione elevato, in linea teorica potrebbe giustificare una risposta limitata ad una terapia di tipo endocrino[12].

Nel nostro studio, invece, questa logica non viene confermata; probabilmente la spiegazione non è da ricercarsi solo nelle caratteristiche biologiche del tumore, ma anche nelle dinamiche molecolari della cellula neoplastica. Al momento non è possibile dare una risposta univoca al riguardo: indagini molecolari (isoforme recettoriali, varianti proteiche), geniche (c-erbB-2, p53) e biologiche (indici di proliferazione, grado di differenziazione tumorale) devono ancora essere adeguatamente condotte per poter delineare una conclusione più certa sui fattori predittivi della risposta all'ormonoterapia.

L'elemento conclusivo che emerge dallo studio è comunque il ruolo di Ki-67 come fattore prognostico indipendente ed aggiuntivo rispetto ai parametri prognostici classici; esso potrebbe contribuire alla definizione di nuovi modelli multiparametrici per la stratificazione del rischio in pazienti con carcinoma mammario N_0.

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Eur. J. Oncol., vol. 8, n. 1, pp. 53-54, 2003

Carboplatinum-related hepatotoxicity: a case report

Tossicità epatica indotta da carboplatino: un caso clinico

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Summary

One of the treatment options of advanced ovarian cancer is the combination of cyclophosfamide and cisplatinum or carboplatinum. Platinum compounds and alkylating agents are rarely responsible for hepatic toxicity. We report a case of a rare manifestation of hepatotoxicity in a patient treated with carboplatinum administered at standard doses. Eur. J. Oncol., 8 (1), 53-54, 2003

Key words: **ovarian cancer, carboplatinum, hepatotoxicity**

Riassunto

La combinazione di ciclofosfamide e cisplatino o carboplatino è considerata un'opzione terapeutica standard nel trattamento del carcinoima ovarico avanzato. I composti del platino e gli agenti alchilanti raramente sono responsabili di tossicità epatica. Viene riportata una rara manifestazione di epatotossicità in una paziente trattata con carboplatino a dosi standard. Eur. J. Oncol., 8 (1), 53-54, 2003

Parole chiave: **cancro ovarico, carboplatino, epatotossicità**

Introduction

The combination of cyclophosphamide with cisplatinum or carboplatinum was considered a standard regimen for the treatment of advanced ovarian cancer as recently as a few years ago. The toxicity of this schedule is usually mild and is well documented[1, 2].

Herein we report an extremely rare manifestation of hepatotoxicity in a patient with ovarian cancer treated with carboplatinum and cyclophosphamide that we infer to be associated to carboplatinum idiosyncrasy.

Case report

A 62-year-old woman with bilateral ovarian endometrioid adenocarcinoma (FIGO III C) was treated 4 years ago, in an other institution, with carboplatinum (AUC 4) and cyclophosphamide (600 mg/m^2).

After the second cycle, the patient developed an acute hepatotoxicity with a dramatic increase in the value of the following liver function tests (LFT): serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), γ-glutamyl transpeptidase (γ-GT), direct bilirubin (D-BIL) and total bilirubin (T-BIL) (Table 1). Hepatitis virus markers were negative. The patient was immediately hospitalized until resolution of hepatic toxicity; no evidence of diseases other then toxic hepatitis was found. Because of this, antineoplastic treatment was suspended, but progression of disease was observed 3 months later. The patient then chose to be treated with the so called "Di Bella protocol". The treatment lasted 6 months, and no other signs of acute hepatotoxicity were registered. Later, however, a further progression was documented, and the patient was submitted to a second-look laparatomy in our institution. Treatment with paclitaxel (60 mg/m^2/week) was finally programmed.

Discussion

Platinum compounds and alkylating agents are rarely responsible for hepatic toxicity[3]. Cyclophosphamide is metabolized in the liver, but only a few cases of elevation of the values of LFT have been reported. Cisplatinum is not hepatotoxic at standard doses[4], and at higher doses an increase in LFT levels, especially SGOT and SGPT, has also been rarely reported[5].

Pervenuto/Received 28.6.2002 - Accettato/Accepted 21.10.2002
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Table 1 - Mean values and standard deviation (SD) of liver function tests before, during and after the second cycle of chemotherapy

Indices	Pre-treatment Mean (SD)	During treatment Mean (SD)	Post-treatment[(a)] Mean (SD)
SGOT (UI/l)	8.3 (1.5)	30 (18.4)	660 (179)
SGPT (UI/l)	9.3 (0.6)	49.5 (37.5)	1052 (302)
γGT (UI/l)	40.7 (4.7)	38 (1.4)	163 (45)
T-BIL (mg/dl)	0.4 (0.003)	0.6 (0.2)	4.8 (7.8)
D-BIL (mg/dl)	0.5 (0.003)	0.3 (0.06)	6 (9)

[(a)] Day 6-16 after the second cycle of chemotherapy

Moreover, carboplatinum is usually less hepatotoxic then cisplatinum; however, there is a single report of autopsy-documented hepatic veno-occlusive disease in a patient who received high-dose carboplatinum[6].

In our report, the patient developed an acute hepatotoxicity after the second cycle of treatment with carboplatinum and cyclophosphamide at standard doses. In fact, her liver tests showed an increase of SGOT, SGPT, γGT, T-BIL and D-BIL (Table 1). A daily control of LFTs was performed during hospitalisation and thereafter on a weekly basis for two months. Eighteen results were available for this report. These values indicate a grade 4 hepatic toxicity according to the hepatic Common Toxicity Criteria of the National Cancer Institute[7]. The high values observed are usually related to a viral-like hepatitis, but viral infections were excluded. Thus the clinical picture of this patient was compatible with an abnormal reaction such as drug-induced hepatic necrosis with inflammatory reaction due to delayed hypersensitivity to treatment[8].

It is important to underline that this patient, after the resolution of the episode of hepatotoxicity, was treated for disease progression with the so-called "Di Bella protocol". This protocol does not include carboplatinum but it does include, among other drugs, cyclophosphamide, even though at lower doses (50 mg/die) than the standard chemotherapic treatment. No hepatotoxicity was registered during this treatment. Since neither hepatic necrosis with inflammatory reaction nor delayed hypersensitivity are dose-dependent[8], cyclophosphamide is unlikely to be the drug responsible for the patient's acute reaction.

These data suggest that carboplatinum, administered at standard doses, may be the causal agent for the episode of hepatic toxicity. Since this drug is included in a large number of chemotherapeutic protocols, we believe that awareness of the information reported in our study may improve the clinical management of cancer patients.

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Eur. J. Oncol., vol. 8, n. 1, pp. 55-57, 2003

Sindrome di Pancoast ed infiltrazione del midollo spinale da mesotelioma maligno della pleura: descrizione di un caso in una donna esposta ad asbesto

Pancoast syndrome and spinal cord infiltration by malignant pleural mesothelioma: a case report in an asbestos-exposed woman

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Riassunto

Viene descritto un caso di mesotelioma maligno della pleura (MMP) asbesto-correlato in una donna, trattato con chirurgia, chemioterapia e radioterapia palliativa. Il caso è stato caratterizzato da una lunga sopravvivenza di 40 mesi e da un'evoluzione finale inconsueta con la comparsa di due gravi complicanze, una recidiva apicale del MMP con sindrome di Pancoast ed un'infiltrazione del midollo spinale a livello di D2 - D3 con paraparesi. Eur. J. Oncol., 8 (1), 55-57, 2003

Parole chiave: **mesotelioma della pleura, asbesto, donna, midollo spinale, sindrome di Pancoast**

Summary

A case of asbestos-related malignant pleural mesothelioma (MPM) in a woman treated by surgery, chemotherapy and palliative radiotherapy is described. The course of the disease has been characterized by a long survival time of 40 months and by two rare and severe terminal complications, an apical relapse of the mesothelioma with a Pancoast syndrome and a spinal infiltration at D2 - D3 level with paraparesis. Eur. J. Oncol., 8 (1), 55-57, 2003

Key words: **pleural mesothelioma, asbestos, woman, spinal cord, Pancoast syndrome**

Introduzione

Generalmente la presentazione clinica del mesotelioma maligno della pleura (MMP) e la sua evoluzione sono caratterizzate dal progressivo aggravamento della sintomatologia toracica (dispnea, dolore, tosse), talora accompagnata da quella sistemica (febbre, astenia, calo di peso), che tardivamente, può complicarsi con i segni dell'invasione peritoneale o pericardica. Occasionalmente, però, l'evoluzione può essere atipica e determinare la comparsa di quadri clinici inconsueti; tra questi l'interessamento del solco superiore e quello del sistema nervoso sono stati segnalati in rari casi. Nel presente lavoro viene descritto un caso di MMP la cui evoluzione, nella fase avanzata della malattia, è stata caratterizzata da una sindrome di Pancoast e da un'infiltrazione neoplastica del midollo spinale.

Pervenuto/Received 17.6.2002 - Accettato/Accepted 16.10.2002
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Descrizione del caso

La paziente, donna di 66 anni, venne ricoverata presso l'Unità Operativa di Medicina dell'Ospedale di Monfalcone a causa della recente comparsa di dispnea a riposo e di febbre (fino a 38°C), senza tosse, dolore o calo di peso. Non riferiva alcun precedente morboso di rilievo. Dapprima, dai 29 ai 32 anni, aveva lavorato come operaia presso un cotonificio, quindi, dai 35 ai 55 anni, presso i cantieri navali di Monfalcone in qualità di addetta alla mensa. Dall'età di 20 anni fumava 10 sigarette al giorno. All'esame obiettivo si presentava in buone condizioni generali; al torace erano presenti i segni di un massivo versamento pleurico destro; non altri reperti di rilievo. Il radiogramma del torace confermava la presenza dell'esteso versamento pleurico destro e la TC del torace, oltre al versamento pleurico, evidenziava anche un ispessimento pleurico al campo polmonare superiore ed a livello diaframmatico; all'esame citologico del liquido pleurico erano presenti rare formazioni papillari composte da cellule atipiche di verosimile natura mesoteliale ed il quadro deponeva per un mesotelioma. La paziente venne sottoposta a toracotomia con pleurectomia parietale e decorticazione del polmone destro e la diagnosi istologica fu di mesotelioma maligno della pleura di tipo misto; successivamente venne trattata con 5 cicli di chemioterapia con carboplatino e gemcitabina. In occasione della rivalutazione eseguita al termine della chemioterapia, la paziente si presentava in buone condizioni generali, non lamentava alcun sintomo toracico, ed il quadro TC toracico era stazionario (ipoespansione dell'emitorace destro, ispessimenti pleurici costo-vertebrali e diaframmatici, as-

senza di versamento pleurico) rispetto a quello immediatamente successivo all'intervento chirurgico. La paziente venne quindi seguita con un regolare follow-up clinico e strumentale mantenendosi asintomatica ed in buone condizioni, tanto da condurre una vita normale per 32 mesi dall'esordio della malattia, fino alla comparsa di una sintomatologia dolorosa localizzata alla parte superiore dell'emitorace destro ed alla spalla, accompagnata da una ripresa della dispnea da sforzo. In tale occasione alla TC era evidente una lesione solida localizzata all'apice polmonare destro che infiltrava la pleura e la parete toracica (fig. 1), e clinicamente la fossetta sovraclaveare destra appariva occupata da una massa dura e fissa. La recidiva del MMP venne trattata con radioterapia palliativa sulla regione apicale destra (20 Gy in 5 sedute) con buona riduzione del dolore. Dopo altri 4 mesi la paziente iniziò a lamentare un deficit ingravescente della deambulazione associato ad un'estesa riduzione della sensibilità cutanea che dalla parte superiore del tronco (linea intermammillare) si portava sino alle estremità inferiori. L'esame neurologico evidenziava una marcia paraparetica flaccida con iperreflessia osteotendinea diffusa ed ipoestesia tatto-dolorifica con livello sensitivo in D8. La TC del tratto dorso-lombare della colonna risultava negativa, mentre la RMN della colonna dimostrava la presenza di alterazioni morfologiche e di segnale a livello di D2 e di D3, nonché di tessuto neoformato che, oltre a coinvolgere i corpi vertebrali descritti, si estendeva all'interno del canale vertebrale, in particolare a livello del corpo di D2, circondando a manicotto il midollo (fig. 2).

La paziente fu trattata con steroidi ad alte dosi ma nei successivi quattro mesi il quadro neurologico peggiorò progressivamente con l'instaurarsi di una paraparesi irreversibile. La paziente morì a distanza di 40 mesi dall'esordio clinico del MMP.

Discussione

Il caso descritto si presta ad alcune considerazioni.

La prima riguarda il sesso, in quanto l'incidenza del MMP nelle donne, storicamente poco colpite, sta dimostrando da alcuni anni un netto incremento. Le cause non sono note. Ipotizzabile un più lungo periodo di latenza del MMP nel sesso femminile quale conseguenza del minor livello di esposizione all'asbesto. Molto bassa, infatti, è l'esposizione domestica, e bassa può essere anche un'esposizione lavorativa marginale, come quella che si era verificata nella nostra paziente. Se questa interpretazione è veritiera, gli effetti dell'asbesto nelle femmine sono destinati a costituire un fenomeno epidemiologico più tardivo rispetto a quello osservato nei maschi, per cui, nei prossimi anni, si assisterà ad un netto incremento del numero di donne malate di MMP. Ci si può attendere, quindi, una variazione del rapporto maschi/femmine che, nella nostra casistica, era, in uno studio degli anni '90, di 10,4[1].

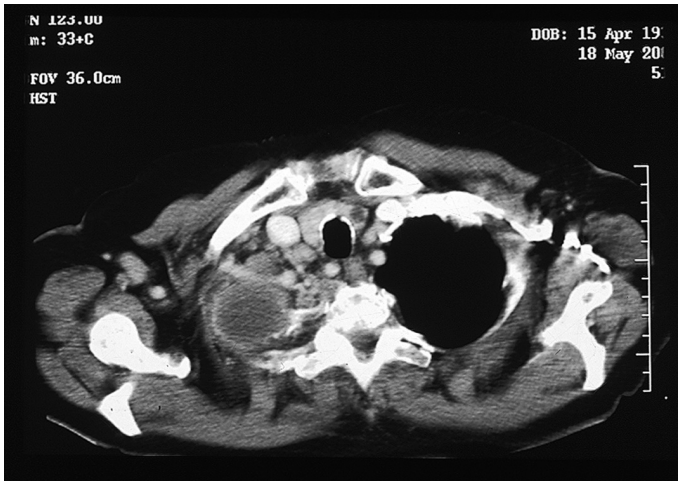

Fig. 1. TC del torace. Lesione solida localizzata all'apice polmonare destro che infiltra la pleura e la parete toracica

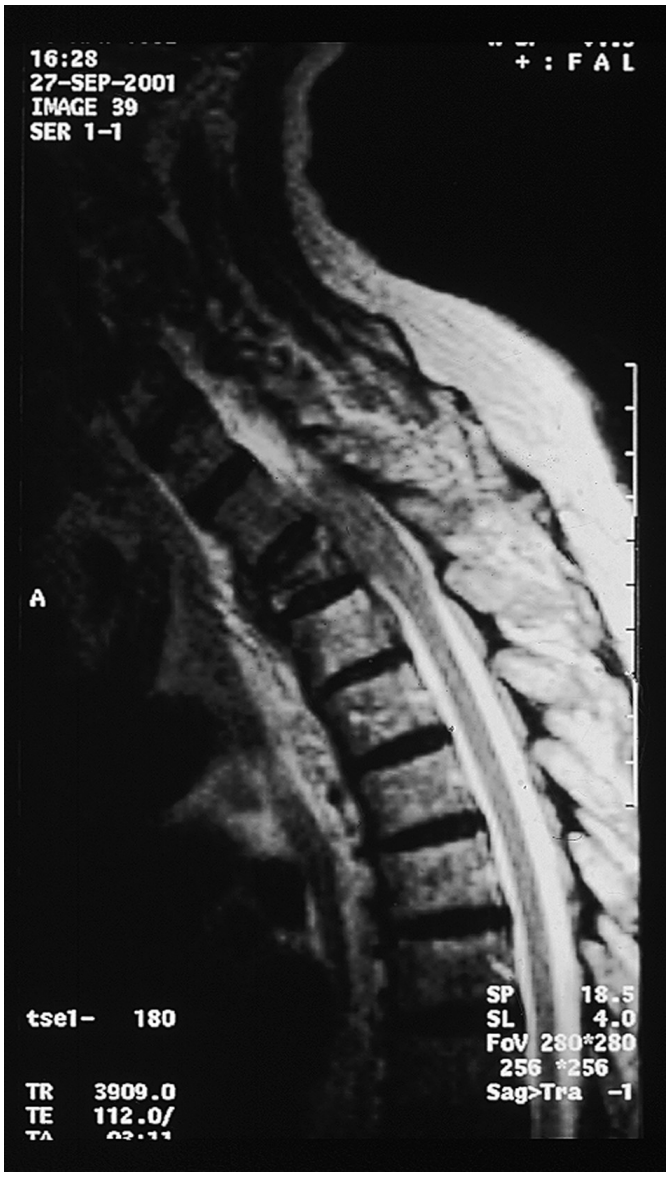

Fig. 2. RMN del midollo. Alterazioni morfologiche e di segnale a livello di D2 e di D3 con tessuto neoformato che coinvolge gli stessi corpi vertebrali e si estende all'interno del canale vertebrale circondando a manicotto il midollo

La seconda riguarda il decorso relativamente lento della malattia, con una sopravvivenza di 40 mesi, ben superiore alla sopravvivenza media di 13 mesi da noi osservata[1]. Analizzando i fattori prognostici del nostro caso[2] si può osservare come in questa paziente tali fattori erano tutti favorevoli (buon *performance status*, stadio I, età non avanzata, istotipo non sarcomatoso), ed hanno indubbiamente influenzato in senso positivo il decorso. Difficile altresì, stanti i dubbi che tuttora persistono sull'efficacia della terapia nel MMP, attribuire anche alla terapia un effetto favorevole. Comunque, da qualche anno c'è la sensazione di un'evoluzione più lenta del MMP in molti pazienti, forse proprio grazie ad una maggior efficacia delle terapie praticate.

La terza considerazione riguarda l'evoluzione della fase finale del mesotelioma. Infatti, ancor più della lunga durata della sopravvivenza, colpiscono le sue caratteristiche. Se per ben 32 mesi la malattia è rimasta asintomatica e del tutto priva della sua abi-

tuale sintomatologia, negli ultimi 8 mesi si sono manifestate complicanze inusuali e molto sfavorevoli.

La prima complicanza è rappresentata da una sindrome di Pancoast, con la sua caratteristica sintomatologia dolorosa legata alla sede apicale della recidiva. Questa, descritta in un nostro precedente caso quale inconsueta modalità di esordio del MMP[3] e successivamente in un altro caso segnalato da Autori giapponesi[4], è stata ben controllata dalla radioterapia palliativa. Anche in questa occasione, così come in altri casi osservati personalmente, in cui era stato possibile controllare con la radioterapia il dolore da lesioni nodulari della parete toracica da MMP, la radioterapia ha svolto un favorevole effetto palliativo.

La seconda complicanza ancor più rara e molto più grave, è stata l'infiltrazione mesoteliomatosa del nevrasse con paraparesi irreversibile. La possibilità di un coinvolgimento del sistema nervoso da parte del MMP, un tempo considerata del tutto improbabile, è oggi riconosciuta come un'evenienza possibile, ancorché rara. In effetti il MMP è stato lungamente ritenuto una malattia ad accrescimento locale e solo lo studio autoptico di ampie casistiche ha permesso di verificare come in realtà anche nel MMP le metastasi siano frequenti, anche se poco evidenti sul piano clinico. Infatti, anche in fase avanzata, la sintomatologia del mesotelioma pleurico è dominata dal progressivo coinvolgimento respiratorio al quale si affiancano quello addominale e talora quello pericardico. L'interessamento del sistema nervoso può verificarsi in varie modalità; accanto alle metastasi cerebrali troviamo la rara carcinomatosi leptomeningea, di cui in passato descrivemmo un caso[5], la degenerazione cerebellare subacuta[6], nonché l'infiltrazione diretta del nevrasse descritta in rari casi[7]. Quest'ultima è stata la modalità evolutiva che si è verificata nella nostra paziente. Sussiste infatti una precisa corrispondenza topografica tra il livello della recidiva polmonare e quello del coinvolgimento midollare. In questo caso il tessuto mesoteliomatoso ha interessato per continuità il midollo spinale, penetrando all'interno del canale midollare attraverso i forami intervertebrali e circondando a manicotto il midollo spinale. A nostra conoscenza si tratta di una complicanza molto rara e intrattabile che conduce ad un progressivo peggioramento del deficit sensitivo e motorio fino alla morte.

Ringraziamenti

Si ringrazia il Sig. Stefano Braico, Tecnico Sanitario di Radiologia Medica, per il contributo offerto per le immagini radiologiche.

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via Guerrazzi, 18 - 40125 Bologna, Italy
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via Coduro, 1/B - 43036 Fidenza (PR) - Italy
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