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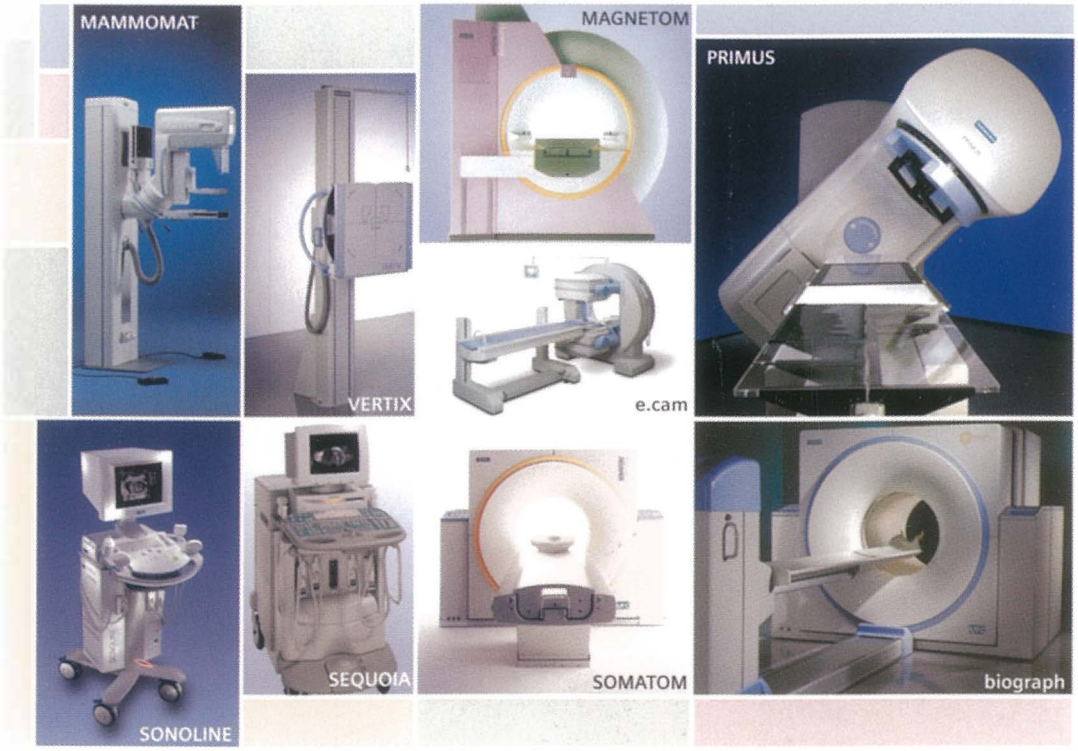

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CONTENTS

Radiology and Oncology is covered in *Biomedicina Slovenica, Chemical Abstracts, EMBASE / Excerpta Medica, and Sci Base*

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Ten years of the journal Radiology and Oncology some bibliometric evaluations

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Background. *Bibliometrics and its methods are a useful set of tools for analysing a scientific journal's relative position in the field. By measuring different quantitative data and comparing them with other journals in the field, certain decisions can be made as to the future of the journal.*

Objectives and methods. *We thought as appropriate to take last ten years of Radiology and Oncology (1992-2001) and put that content to double scrutiny: first, by applying various quantitative measurements to the journal's content to get a more objective picture of the whole and of its development in the past ten years; then by additionally comparing it to another international journal from the field and of similar orientation, Neoplasma, to illustrate if differences and/or similarities between the two are in favour of or detriment to Radiology and Oncology.*

Results and conclusion. *Results show that Radiology and Oncology has been progressing in the right direction, but that extra efforts should be made by the editors and the editorial board to attract more articles per issue and to gradually increase the share of experimental articles to boost its impact in the field. Also, to improve its visibility, editors, reviewers and also authors that publish in Radiology and Oncology could consider citing the articles published in this journal, in the articles published elsewhere, when appropriate.*

Key words: radiology; medical oncology; periodicals; bibliometrics

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Introduction

Rationale

The aim of the study was to establish, and possibly define, the position of the scientific journal *Radiology and Oncology* and its relative importance in the field, by applying relevant bibliometric measurements.

Bibliometrics has, for various reasons, been widely discussed in scientific circles recently,[1,2] especially two of its best known

methods, citation analysis and impact factor, a journal's relative weight in scientific community. Both methods are in a way defining the position of a scientific journal in a highly competitive, if not sometimes controversial,[3,4] market of published scientific communication. The nature and importance of citation analysis have not always been given equally welcome reception, since bibliometrics started its life as an independent scientific discipline back in the 60s. However, the results were always met with unhidden interest and due concern.[5] Bibliometric methods - at least some - have been at times widely disputed as well as defended: bias in favour of scientifically important nations or countries and/or English language, overimportance given to the tools provided by ISI[i], primarily its two important databases, SCI[ii] and JCR[iii], which exclude most of the journals from non-English speaking world, and journals not published in English language, etc., to name just a few.[6] Still, all bibliometric methods can be used quite safely and effectively, bearing the only reproach which all other quantitative research methods are burdened with, so well epitomized by Disraeli's[iv] refering to the statistics: »There are lies, bigger lies, and statistics!«

By analysing citations, i.e. bibliographic references or sources of information as they are sometimes called which appear at the end of articles, we may evaluate the importance of published articles, and consequently of the journals that publish them, and show their relative weight in peer circles, as well as measure their relevance in the process of exchange of information among scientists.[7] However, when comparing various larger environments, like states or countries and research communications they generate, bibliometric analysis must take into consideration many complex factors affecting such environments, like fair comparison of the scientific development through time, local science policy that does not always have positive impact on scientific community, the fact that scientific research has increasingly become internationalized, with transborder cooperation involving many different scientists from different cultural backgrounds, etc.[5]

To measure and evaluate the same for Slovene scientific journals is a much more complicated task, since until recently[v] no Slovene research journal had been included in SCI that regularly measures the relevance of selected scientific journals for, and their impact on, the research community worldwide. Citation analysis data on Slovene medical journals, for instance, would serve many purposes, not the least to establish in a more objective way their position and role in the worldwide process of scientific communication exchange.[8] Comparing Slovene medical journals among themselves may be completly impractical, if not downright impossible and would, in any case, require extreme caution to exclude the possibility of contents or disciplines being compared that can not be so. It is therefore necessary to implement a certain level of precaution and to scale down the area of comparison to possibly a very similar, if not the same, specific subject of research or activity.

Since there are not many research centres in Slovenia that would be deeply involved in oncology research, let alone scientific journals that would publish articles in this area, international comparisons are the obvious choice to establish the position of the journal in the field, like *Radiology and Oncology*. Actually, there was an attempt to assign impact factors to the medical journals published in Slovenia, based on recorded articles in the database BIOMEDICINA SLOVENICA.[8] However, this was only an experimental enterprise which brought some interesting and applicable solutions for further consideration.

Genealogy

The journal *Radiology and Oncology* represents a logical continuation of the now defunct sci-

entific journal *Radiologia Iugoslavica*, that was published by The Yugoslav Association of Radiology and The Yugoslav Association of Nuclear Medicine (later to merge into The Yugoslav Association of Radiology and Nuclear Medicine), appearing for the first time in 1964. Initially, it served the purposes of publishing proceedings or papers from various national meetings and conferences in the field, but soon became more and more a scientific journal with its own set of articles. In the first few years the articles were written and published in various languages of the Yugoslav federation, but later accepted and published articles in all proposed languages. The Association's offices always were at the Institute of Oncology in Ljubljana, and the editorial board mostly comprised Slovene oncologists: S.Plesničar, T.Benulič, J.Škrk, P.Soklič, and B.Tavčar. In the first few years (1964-1968), the journal went through some difficult periods regarding financial support, as well as editorial and organizational matters[vi], however, after vol.4 (1969), the journal was well established and appeared regularly in one volume per annum, comprising 4 regular issues and irregularly published supplements that in most cases brought proceedings from national and international conferences. This continued until vol.25 (1991) when, on account of the break-up of Yugoslav federation, the communications between members of the Association became very difficult or died out completly and the journal stopped being published. From among the membership a new editorial team grew up, which was more flexible, had new ideas and above all had experience with international journals as all editors regularly published elsewhere. In 1992 and with vol.26, the journal changed the name into *Radiology and Oncology*, the editors were the same as with the last volumes of *Radiologia Iugoslavica*, however the design and looks of the journal were changed, though the numbering of volumes has been kept and basic subject orientation was continued.

The journal today does not resemble in any way its predecessor, except maybe in format which is still a book-size (the upper limit of what in the publishing industry used to be called *octavo*), a feature typical for many journals with a Yugoslav pedigree[vii]. The design and looks are much more appealing, more graphics and photos accompany articles, the paper and print are of better quality (with one or two exceptions, perhaps). The journal is by now an official journal of the Association of Radiology and Oncology, affiliated with Slovenian Medical Association, Croatian Medical Association, Societas Radiologorum Hungarorum and Italian Society of Medical Radiology. The editorial policy is mostly run by T.Benulič, G.Serša (who soon becomes the editor-in-chief), and V.Kovač. Later this group is joined by U.Smrdel. The offices of the journal remain in the Institute of Oncology in Ljubljana, Slovenia. The journal continues as a quarterly, with irregularly published supplements which in many cases are entirely in Slovene language, while the articles in regular issues are now all in English, a clear indication that the journal intends to broaden or extend its authorship and readership populations. The articles are grouped and published in rough subject categories[viii] and each issue also brings reports from meetings, conferences and/or symposia (these are not included into the analysis below), announcements of future conferences, book or new journal reviews (also not included into analysis). The index of each volume (by authors and by subjects) is published in the last issue of the running volume and also includes supplements[ix], while the names of participating reviewers are given at the beginning of each index listing.

In 1992, an entirely separate publication was published, entitled **Advances in *Radiology and Oncology*** (editors were G. Serša, T. Benulič, V. Kovač), and though it resembled the then upcoming and still undisclosed new journal *Radiology and Oncology* in

almost all its outer features (paper and print quality, colour and graphic design), it did not have any direct link with the later journal itself, nor was it its supplement. The publication was issued to commemorate the 25th volume of *Radiologia Iugoslavica* and brought together, under one title, the papers from some of the best known world experts in oncological radiology, a kind of state-of-the-art at the time. This publication may, however, be to some extent considered as a link between the old journal with the old editorial policy, and the new journal with its new outlook (of which the publication is a precursor) and new and fresh editorial ideas.

Methodology and types of analyses

Bibliometric analyses of various features of publication were made, using three time probes, i.e. three different years, from the span of 10 years of publishing, i.e. 1992 being the first year under the new title, 1996, and 2001. Only professional articles were considered, while meeting reports, book reviews and letters to the editor were excluded as already mentioned above. Bibliometric methods were applied with the aim to show the professional growth and the quality of articles through time span of ten years and in some cases comparisons were made with *Neoplasma*, an international journal, similar in the subject orientation, that has already been included in ISI's SCI database and is also covered by MEDLINE, the most important biomedical bibliographic database. These are the two goals that *Radiology and Oncology* has yet to achieve, though international comparison might point to the set of very different reasons which may have little to do with contextual or subject quality levels but nevertheless seem to have an important impact on decisions as to who is let in (i.e. MEDLINE) and who remains waiting outside.

Bibliometric analyses of articles

Two important indicators were measured for both journals: the number of articles per volume in a given period and their diversity expressed by the type of article and article orientation. Since *Neoplasma* does not have the practice of assigning articles to specific subject groupings within the journal while *Radiology and Oncology* does, articles from both journals were therefore grouped under their different types and orientations, based on the classes from the MeSH Thesaurus[x]. This analysis aimed to show the scientific orientation of the articles on one side, and of the journal as a whole on the other.

Bibliometric analyses of authors

The methods used in this type of analysis were applied to record the changes of and the variety in, the authors' population as one of the basic indicators of importance that the authors give to their publishing in a particular journal and in a particular field; of variety of their nationality or affiliation, and the level of cooperative writing as means of securing publishing of results of research as has recently been claimed in the literature from the field.[9,10]

Bibliometric analyses of citations

Methodologies used here are among those that general public usually think of when bibliometrics is mentioned and indeed, various types of citation analysis are sometimes taken almost as a synonym for bibliometrics. The aim here is to survey some classical attributes of bibliometric measurements that point to the professional level of articles in one journal and compare them with general trends in similar journals elsewhere (in this case, with the bio-medical journals). This can be deduced by analysing the age of citations, types of literature sources used in citations, the languages in which citations were published, the extent of self citations being practised, etc. Bibliometric theory suggests that this last is

also an indicator of the ambitions present in the editorial policy of the journal to boost the importance of the product and consequently be included into large and important databases and information sources that are valued and frequently consulted by the peers in the profession, which in turn rewards the journal by new citations and consequently higher ratings in the field.[11]

Results and discussion

Articles

By analysing data in Table 1 we can see that *Radiology & Oncology* was fairly consistent in the number of articles published per year, i.e. the number is almost always between 40 and 50 (r = 48,4 article/year). There are two exceptional years, 1994 with 62, and 1997 with 83 articles. Both were results of conferences, some articles of which found their way into the journal's regular issues[xi].

Though *Neoplasma* is a bi-monthly and one would normally expect that it publishes more articles on account of its frequency, the closer look shows that the two additional issues per year can not be the main reason for such a difference but that evidently, every issue of *Neoplasma* brings more articles than *Radiology and Oncology*, an expectation that is confirmed by comparing the total number of articles published in the period 1992-2001 in *Radiology and Oncology* and the total number of articles published by *Neoplasma* only in the three compared years (1992; 1996; 2001): in the three years *Neoplasma* published almost half as much articles as *Radiology and Oncology* in ten years. Also by comparing the figures for the years chosen for analysis in both journals we can see that, for instance, in 1992 *Radiology and Oncology* published just above 10 articles/issue on average, while the same calculation for *Neoplasma* gives us good 11 articles. The difference of 1 article/issue remains steady also in 1996 (11 for *Radiology and Oncology*, 12 for *Neoplasma*), while it increases considerably in 2001 (less than 10 per issue for *Radiology and Oncology*, and over 14 per issue for *Neoplasma*).

Table 1. No. of articles per year

	Radiol Oncol	*Neoplasma*
Year	Articles / year	Articles / year
1992	**41**	**68**
1993	43	
1994	62	
1995	46	
1996	**44**	**72**
1997	83	
1998	44	
1999	40	
2000	42	
2001	**39**	**86**
Total Radiol Oncol	*484*	
Total (92+96+01)	**124**	**226**

Is there a lesson to be learned? Very probably - the figures for *Radiology and Oncology* for the years after the record high 1997 show a consistent decline in the number of published articles per annum which may point to several reasons: weak response by the authors to publish in the journal; the changes in the editorial team, or the change of the editorial policy which might not have been wholeheartedly accepted by potential authors. On the other hand it may also point to the old problem - the authors' population have matured and the same individual researchers who got a chance to publish their research results from their early enterprises in this journal (which, by the way, has always been one of the important missions of the journal), have joined different teams and are now bound to publish together with their new team colleagues in other international journals that expectedly have more impact on the profession, since publishing in high impact publications is favoured by the funding agencies and evaluators.[9,12]

One way of increasing journal's impact might be to increase the number of experi-

mental articles. As Table 2 shows, *Neoplasma* has a significantly higher percentage of such articles than *Radiology and Oncology*. It seems that in the field of oncology, experimental articles tend to receive more citations than other articles, which consequently boosts the impact factor of such journals. Therefore higher crop of original and experimental articles that compete for publishing space, higher quality of selected articles for publication, and consequently a stronger appeal for authors from other parts of the world to publish in the journal. As soon as the journal gets accepted into important international databases, it is significantly more attractive to the authors. It would be therefore advisable for *Radiology and Oncology* to increase the number of articles per issue and/or volume and at the same time to publish more experimental articles.

Authors

There is a general trend in STM[xii] category of journals towards expanded authorship, i.e. there are very few articles published in those journals nowadays that would be signed only by one or two authors. On one hand this represents a healthy feature of the medicine as a discipline in itself, i.e. the convergence of scientific disciplines and interconnected teamwork of many researchers from many fields towards the same goal; on the other, it may hide a much more mundane reason, i.e. being the result of planned response to the conditions put in place by the funding agencies: more researchers share authorship - more credibility the research work has, higher position on the future priority lists for funding.[9,11,12] This may sometimes lead to exaggeration and consequently, hyperauthorship.[10,13]

Still, recent studies show[10,14] that the average number of authors per article for the journals screened by SCI increased from 1,83 in 1995 to 3,9 in 1999 per article[10,12], while an analysis made for the *British Medical Journal* established that the articles published in that journal in the period 1975-1995 showed increase in the number of authors from 3,2 in 1975 to 4,7 in 1995.[12,13]

As can be seen from Table 3, *Radiology and Oncology* very much experienced similar trends, with only 2,51 authors per article in 1992, increasing to 3,66 in 1996 and reaching almost 4,0 (3,92) in 2001. That such development is the result of the natural development of medicine, as was already explained above, is further witnessed by the results from Table 4: there is no trace of exaggerated authorship as most articles are shared by one, two or at most, seven authors.

Table 2. Articles by type and orientation (based on MeSH classes)

	RADIOL ONCOL			*NEOPLASMA*		
Type of article	**1992**	**1996**	**2001**	**1992**	**1996**	**2001**
- Journal article	85,4%	77,3%	76,9%	98,5%	90,3%	82,6%
- Review	4,9%	9,1%	12,8%	-	5,5%	9,3%
- Editorial	-	-	-	-	-	-
- Letter to the editor	-	-	-	-	-	-
- Case/Clinical trial	9,7%	13,6%	10,3%	1,5%	4,2%	8,1%
- Other*	-	-	-	-	-	-
By orientation	**1992**	**1996**	**2001**	**1992**	**1996**	**2001**
- Diagnostic	53,7%	27,3%	38,5%	27,9%	30,6%	32,6%
- Therapeutic	19,5%	47,7%	41,0%	22,1%	25,0%	29,0%
- Experimental	9,7%	15,9%	15,4%	41,2%	31,9%	25,6%
- Other**	17,1%	9,1%	5,1%	8,8%	12,5%	12,8%

*reports, interviews, obituaries, patents, abstracts, etc.

**etiological, epidemiological, prevention, incidence analyses, etc.

Table 3. Number of authors per year and their average number per article

	Radiol Oncol			*Neoplasma*		
Year	au	art	r	au	art	r
1992	**103**	41	**2,51**	**293**	68	**4,31**
1993	143	43	3,32			
1994	226	62	3,65			
1995	198	46	4,30			
1996	**161**	44	**3,66**	**325**	72	**4,51**
1997	342	83	4,12			
1998	173	44	3,93			
1999	167	40	4,18			
2000	133	42	3,17			
2001	**153**	39	**3,92**	**426**	86	**4,95**
Total R & O	1799	484	3,72			
Total (92+96+01)	**417**	124	**3,36**	**1044**	226	**4,62**

Hyperauthorship tends to include all kinds of junior staff or technicians which did their work as part of the daily routine and therefore their share can not be equally assigned as authorship[15-16,21], or past research team members, which used to share their results with the others while still active. This is bogus and throws bad light on published research results of serious teamwork endeavours[xiii]. It is very positive to see that the editors of *Radiology and Oncology* have not yielded to such trends.

Addditional important feature to consider is the extent of internationalization of authors that publish in a scientific journal. With a few exceptions, most journals welcome the chance to have a colourful mixture of authors from all over the world. Still, in this process some institutes and as well as some researchers tend to develop stronger ties with each other, and consequently are more represented in each other's publications. A fair spread of authors from various institutes and countries of affiliation shows a good editorial policy and is also an indicator that regardless of the all-important inclusion into as many international databases as possible, journals which are presently not contained in all of them are still fulfilling their mission and are selected by many authors from various corners of the scientific arena to publish therein. This can certainly be said for *Radiology and Oncology*, as the results in Table 5 not only show a very even spread of international authors, but Table 6 also confirms, that members who are on the editorial team or members of the editorial board do not enjoy any advantages when being peer-reviewed for publishing or that the editors tend to form close circles of authors who have *card blanche* to publish in the journal, whenever and whatever. Only one member of the editorial team was among the top 6 authors with highest number of articles published in 1996, while in 2001, there was none as there were only 2 au-

Table 4. Articles by the number of participating authors

	Radiol Oncol			*Neoplasma*		
	1992	1996	2001	1992	1996	2001
1 author	16	5	2	1	3	6
2 authors	10	14	8	15	10	8
3 --	2	5	8	16	10	17
4 --	7	5	9	16	17	9
5 --	4	8	3	8	15	12
6 --	1	2	7	3	8	13
7 --	1	1	0	7	4	8
8 --	0	3	0	2	2	3
9 --	0	0	2	3	0	4
10 or > 10	0	1	0	0	3	0

Table 5. Authors by country of their affiliation (at the time of writing)

	Radiol Oncol			*Neoplasma*		
	1992	1996	2001	1992	1996	2001
Australia			1			1
Austria			10	9	5	3
Belarus						1
Belgium					2	
Bosnia and Herzegovina	11					
Brazil					6	4
Bulgaria			9	1	9	
Canada		9	2		1	
China		5				
Croatia	59	35	35	7	9	12
Czech Republic			6	*97	48	114
Denmark		2				
Finland				2		
France				2		6
Germany	5	34	17	6	4	1
Greece		7	4			
Hungary	2		3	1	6	22
India				55	10	
Israel					2	
Italy				7	4	2
Japan				6	6	
Kuwait					5	1
Macedonia FYRO		4	5			
Poland			8	27	53	63
Romania				8		
Russia		2		7	12	
Slovak Republic					93	124
Slovenia	21	61	43		2	15
Spain				11	3	
Sweden		1		3		
Taiwan					12	20
Turkey					4	14
Ukraine				9		
United Kingdom				4	5	1
United States			15	11	5	1
Yugoslavia**	1			20	19	21

*The number given contains both, data for Czech Republic and for Slovak Republic

**The name used for FRY or what is now called Serbia and Montenegro

thors that succeeded to publish more than 2 articles in the journal in that year. This also proves that the editorial team does the effort to allow equal representation to all classes of articles, though this may sometimes act against their ambition to be included in high-profiled international medical database, like MEDLINE. Similar features can be seen in *Neoplasma*, though the relative majority of authors from the Slovak or Czech institutes or/and provinence does hint to, either a slight favouring of domestic authors as compared to *Radiology and Oncology*, or simply to the fact that authors from abroad were less keen to send their articles to be published in the journal in the period reviewed.

Citations

There is a very strong opinion, supported by many empirical research, that citations are the very indicators and the key to evaluating the level of scientific significance of one journal. Rennie[16] quotes de Solla Price[18] who proposed that the articles within each scientific discipline could be broadly classified as »scientific« and »non-scientific«, claiming that »scientific« articles are those that have 10 to 20 citations, and »non-scientific« those without citations, while articles with more than 22 citations were to be treated more as further reading assistance.[17] As much as de Solla Price's theories were supported by empirical research[18], there are actually many motives to be considered when investigating, why authors cite certain works and how many they choose to include into citations.[9]

A look at the results from the Table 7 shows that all articles published in *Radiology and Oncology* fulfill the conditions proposed by the above theory. Actually, absolute numbers showed that some articles did go into excesive citing, but that majority still remain within the relative limits, which may be construed that the journal as such falls into the category of »scientific« in the field. By comparison, Neoplasma seems to be overdoing

Table 6. Top participating authors in articles (frequency >2)

Radiology & Oncology		
1992 (frq)	**1996 (frq)**	**2001 (frq)**
Fučkar, Željko (3)	Bohuslavizki, Karl H. (5)	Bohuslavizki, Karl H. (3)
Ivaniš, Nikola (3)	Brenner, Winfried (5)	Miklavčič, Damijan (3)
Lovasić, Ivan (3)	Clausen, Malte (5)	
Lovrinčević, Antun (3)	Henze, Eberhard (5)	
Perić, Relja (3)	Kovač, Vili* (3)	
Rubinić, Milivoj (3)	Tinnemeyer, Stephan (3)	
	Wolf, Heike (3)	
	Zakotnik, Branko (3)	

* denotes that the author was on editorial board at the time of writing)

Table 7. Number of citations per year and their average number (av) per article

	Radiol Oncol			*Neoplasma*		
Year	cit	art	av	cit	art	av
1992	**545**	**41**	**13,3**	**1441**	**68**	**21,2**
1993	772	43	18,0			
1994	979	62	15,8			
1995	898	46	19,5			
1996	**1141**	**44**	**25,9**	**1854**	**72**	**25,8**
1997	1098	83	13,2			
1998	1083	44	24,6			
1999	719	40	18,0			
2000	827	42	19,7			
2001	**671**	**39**	**17,2**	**2702**	**86**	**31,4**
Total R & O	8733	484	18,0			
Total (92+96+01)	**2357**	**124**	**19,0**	**5997**	**226**	**26,5**

after 1996, when it was still within the values proposed by de Solla Price, while it overflows the limits towards 2001 when it reaches more than 31 citations per article on average.

Besides the number, the age of citations represents another important indicator. It is well known that the aging of the information contained in the articles is directly related to the scientific field from which citations are taken.[5,11,19] Researchers from STM group of journals, with the exception of taxonomy[20], usually do not profusely cite older sources as it is believed that this would dicrease their usability and diminish the importance of the article. Aging is therefore an important factor to consider and scientific disciplines that put 5 years or less as a half-life period[xiv] are fast developing and medicine is one of them.

From the Table 8 it can be seen that the share of fresh research is being more and more prominent among the published articles in *Radiology and Oncology*. If in 1992, citations of up to 5 years of age were almost in equal proportion with those of 5-10 years of age, the proportion of fresh citations grows by roughly 6% every 5 years (36,2% in 1996 and 42,3% in 2001). Similar trend can be traced for *Neoplasma*, though the increase is not so dramatic and shows also a negative trend, as citations in the time frame 5-10 years increase towards 2001, which is quite opposite with *Radiology and Oncology*. The trend therefore is positive for Radiology and Oncology, also by analysing the languages of citations (Table 11), with English overpowering prevalence, especially in the last two test periods, when

Table 8. Citations by age span

	Radiol Oncol			*Neoplasma*		
Age span	**1992**	**1996**	**2001**	**1992**	**1996**	**2001**
0 - 5	26,6%	36,2%	42,3%	32,7%	41,2%	44,1%
5 - 10	24,8%	30,6%	28,3%	33,9%	29,3%	33,5%
10 - 15	21,5%	17,4%	13,3%	16,3%	12,2%	12,1%
15 - 20	10,8%	8,0%	7,6%	7,9%	7,8%	5,2%
> 20	16,3%	7,8%	8,5%	9,2%	9,5%	5,1%

Table 9. Citations by types of bibliographic sources

	Radiol Oncol			*Neoplasma*		
Type	**1992**	**1996**	**2001**	**1992**	**1996**	**2001**
Article	75,8%	89,4%	86,7%	90,6%	92,2%	95,5%
Monograph	16,7%	8,7%	11,1%	8,5%	6,3%	4,0%
Congress	3,8%	1,5%	1,6%	0,7%	1,3%	0,3%
Gray lit.*	3,5%	0,2%	0,2%	0,1%	- -	0,1%
Other**	0,2%	0,2%	0,4%	0,1%	0,2%	0,1%

*Gray litetarure: project reports, internal doctrines, guidelines, expert opinions, reports of consultation meetings, memoirs, sketches of verbatim records, etc.

** Other: mostly electronic sources (excl. articles in e-journals or chapters in e-books), multimedia, graphic material, didactical aids, etc.

citations in authors' local languages dramatically dicrease.

Concerning types of bibliographic sources in citations (Table 9), it is quite clear that journal articles represent the principal source of information to the authors of medical articles. That corresponds with the general trend of increased number of journal titles being published in STM group of disciplines and the rapid increase in the number of articles being published annually in scientific journals. Journals are therefore ***the*** source of choice, while monographs, congress proceedings and gray literature represent only a fraction in overall number of citations. Still, it seems that the authors publishing in *Neoplasma* put even more importance to journal articles as principal information source as their share of over 90% in all three control years is significantly higher than in the same periods for *Radiology and Oncology*. We therefore thought it interesting to see, how high is the level of matching between most cited journals in both publications: as can be seen from the Table 10, only two journals (*Cancer* and *Journal of Clinical Oncology*) are among those that are most frequently chosen as sources for citations by the authors of both journals, while all others do not match. This may point to either different research patterns and specializations of the authors that publish in the two journals, or to a much lower level of similarity of content orientation between the two journals compared. There may be one more reason for such a result: we already mentioned that *Neoplasma* has a higher number of experimental articles, which have a tendency to include higher number of citations, especially those with very high impact factors.

Finally, there remains a question of self-citations. These may appear in two forms: either authors cite their own earlier work in their articles and such citations are not considered as »pure«, or the journal is being cited in the articles it contains. It is that latter form that we decided to look into in our analysis. A normal ambition of every editorial team is to make their scientific journal important among, and achieve recognition in, its own professional circles and be attractive

Table 10. Scientific journals most frequently represented in citations in 2001 (with Impact Factors)

Radiol Oncol (2001)	x-cit.	IF	*Neoplasma* (2001)	x-cit.	IF
Int J Radiat Oncol Biol Phys	33	3.327	Proc Natl Acad Sci USA	247	10,896
Radiology	30	4.759	Cancer Res	113	8,302
AJR Am J Roentgenol	22	1.998	Blood	81	9,273
J Clin Oncol	16	8.530	J Biol Chem	71	7,258
Med Phys	15	2.313	Cancer	61	3,909
Cancer	14	3.909	Br J Cancer	55	3,942
Radiother Oncol	9	2.815	Neoplasma	47	0,637
Eur J Cancer	8	3.460	Mutat Res	44	4,556
Ann Surg	7	6.674	Nature	43	27,955
J Comput Assist Tomogr	7	1.302	J Clin Oncol	40	8,530

Table 11. Citations by language

	Radiol Oncol			*Neoplasma*		
Year	1992	1996	2001	1992	1996	2001
Bulgarian	0	0	0	2	0	0
Croatian	56	17	0	0	0	0
Czech	1	0	3	7	11	0
English	399	1072	647	1409	1816	2693
French	20	5	0	0	5	0
German	35	33	13	10	9	9
Italian	1	1	0	0	0	0
Polish	0	0	0	0	3	0
Rumanian	0	0	0	1	0	0
Russian	0	0	0	3	0	0
Slovak	0	0	0	2	5	0
Slovene	33	13	8	0	0	0
Spanish	0	0	0	5	6	0
Swedish	0	0	0	1	0	0

Table 12. Self-citations

	Radiol Oncol			*Neoplasma*		
	1992	**1996**	**2001**	**1992**	**1996**	**2001**
NO. OF SELF-CIT.	10	9	7	52	57	40
IN % OF TOTAL	1,8%	0,8%	1,0%	3,6%	3,1%	1,5%

for its peers to publish there. One of the manifestations of such importance is to be accepted into carefully groomed lists of journals that are processed by important international databases (MEDLINE, EMBASE, ISI's range of products, etc.). It will not come as a surprise then, that many editorial teams and reviewers expect from the authors who propose articles for publishing to also cite the appropriate articles from the journal they wish to publish in. Such an attitude and policy of the editors should not be considered as being against any moral standards or publishing culture, unless it develops into a condition for the authors, or a »shortcut«, to get accepted for publishing. It should be clear that a certain level of self-citation is always present in every scientific journal.[9]

It is therefore customary in bibliometric analysis of journals to look into this matter as well. Data in Table 12 clearly shows that neither of the two journals have any dramatic developments in that field. Actually, it would be advisable to stimulate the authors a bit more to cite their own published articles in *Radiology and Oncology* in their future works of related subject, regardless where they are accepted for publication. Though such an advice may seem irrelevant at a first glance, it is actually not so, since an independent analysis[12] of the citations in articles that are published in the journals with a high impact factor by some of the authors represented in *Radiology and Oncology* showed, that these authors did not exhibit any bias in citation selection in favour of high impact journals and that the citations in the articles in such journals did not significantly differ from the citations in the articles the same authors got published in *Radiology and Oncology*. Self-ciations, as a dubious policy of the editors, are therefore not an issue with *Radiology and Oncology*.

Conclusions

Results show that Radiology and Oncology is progressing in the right direction, but that extra efforts should be made by the editors and the editorial board to attract more articles per issue and to increase the share of experimental articles to raise its impact. Also, to improve the visibility of the journal, editors, reviewers and also authors that publish in *Radiology and Oncology* could consider citing the articles published in this journal, in the articles published elsewhere, when appropriate. These are two features that stand out from the comparative data for *Radiology and Oncology* and *Neoplasma*. We also noted that there is not such a close similarity between the two journals, though both are from the same filed of medicine, both are originating from Central European publishing space, and both have a long tradition (if *Radiologia Iugoslavica* is taken into account as a precursor). So called »scientifically marginal countries«[6] share the same fate of hardship with non-English scientific journals when trying to enter the all-important lists of journals being screened for inclusion into large databases. However, as recent developments show (see note *v*), the extra efforts invested in tying invisible college network and editorial ambitions can be helpful in achieving such goals.

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Notes

i Formerly, Institute of Scientific Information, Philadelphia, now, with the new owners, just plain ISI

ii Science Citation Index, comprising separate derivatives, SCI - Science Citation Index, SSCI - Social Science Citation Index, and AHCI - Arts and Humanities Citation Index

iii Journal Citation Report

iv Benjamin Disraeli (1804-1881), skilful diplomat and British Prime Minister during Queen Victoria's rulership

v With 2002, *Acta Chimica Slovenica* was included into the list of journals being screened by ISI for SCI and Web of Science

vi First two volumes were published during 1964-1965, then nothing appeared in 1966; the journal got revived in 1967, then again nothing happened in 1968, until vol.4, when it became settled as a regular quarterly

vii Due to Yugoslav (JUS) standards for scientific journals that favoured book-size format

viii Like Computerised Tomography, Diagnostic Radiology, Medical Oncology, Nuclear Medicine, History of... etc.

ix In the annual index, entries for articles from supplements are given in bold

x MeSH - **Me**dical **S**ubject **H**eadings, the most authoritative and best known co-ordinated and controlled list of subject headings for bio-medical literature; developed and maintained by the National Library of Medicine, Bethesda, USA

xi Conference proceedings were otherwise published in yearly supplements (usually one or two) following the general policy and practice of medical journals.

xii **S**cience, **T**echnology, and **M**edicine

xiii That is why some important medical journals, i.e. *New England Journal of Medicine*, recently started the practice of requesting the authors to actually assign the portion of authorship share for each participating author signed under the article

xiv Half-life denotes the time after which half or more of published material will not be cited again and is considered to be obsolete.

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Unexpected diagnosis for preauricular swelling - two case reports

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Background. *Preauricular swelling in children may be associated with a wide range of pathology. The history, clinical presentation and imaging features of such swellings may be non-specific. Sometimes it can be caused by underlying bone lesion.*

Case reports. *We report about two children who were admitted to the hospital with swelling in the preauricular region and an unexpected final diagnosis. We found aneurismal bone cyst and central giant cell granuloma, respectively.*

Conclusions. *Awareness of such lesions is important to avoid diagnostic errors and a potential mismanagement. These lesions are often difficult to differentiate on the basis of their radiographic features alone. A high-resolution US enables an accurate analysis of soft tissue and helps in the differential diagnosis. It also enables an accurate location of the lesion, which helps to avoid a wrong interpretation based on the clinical finding only. The CT-scan performed afterwards provides necessary information for the assessment of location, structure and size of the lesion.*

Key words: bone cysts, aneurismal - ultrasonography; granuloma, giant cell; tomography, X ray computed

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Introduction

The aneurismal bone cyst (ABC) and central giant cell granuloma (CGCG) of the jaws are usually seen involving the posterior mandible.[1-3] Due to their preauricular location they can be confused with other lesions presented as preauricular swelling such as lymphadenitis or parotitis. The imaging features, both the ultrasound (US) and comput-

ed tomography (CT), of these mandibular lesions are helpful in establishing a differential diagnosis, although microscopic tissue evaluation is generally necessary to accurately identify the lesion.

Case 1

An 11-year old male child was admitted with signs of the swollen right preauricular region with light pain and leukocytosis. It was treated as parotitis or lymphadenitis and antibiotics were prescribed.

After the therapy, the swollen area was still obvious; a fine needle aspiration biopsy (FNAB) was performed and it showed a mass of old and new erythrocytes, phagocytes, cytophages and some multinuclear histiocytes - the differential diagnosis was cavernous haemangioma or hemorrhagic cyst of the parotid gland. FNAB was repeated two more times and each time the same findings were found.

Two months later, when the swollen area showed no signs of the retreat, US and CT were preformed.

US showed a complex mass containing anechoic areas separated by fibrous tissue (Figure 1).

Precontrast CT (GE Sytec 3000) showed the expansive cystic mass of the processus condylaris of the mandible with multiple fluid-fluid levels, suggesting the diagnosis of *ABC*. Contrast CT scans showed the enhancement of the septa, which helped to delineate them from the fluid they contain (Figure 2). The segmental resection of the jaw was followed by the orthodontic treatment.

Case 2

A 9-year old boy complained of the pain and swelling of the right preauricular region, one week after a slap to the face.

US examination showed the expansive soft-tissue mass of the *processus condylaris of the mandible* (Figure 3).

Laboratory tests showed normal calcium, phosphorus, and alkaline phosphatase levels, a normal parathyroid hormone level (PTH), and no circulating PTH-related peptide (PTH-rP).

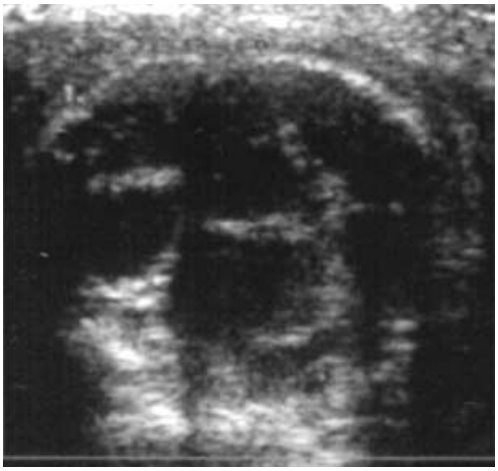

Figure 1. Aneurismal bone cyst. Transverse sonogram of the processus condylaris of the mandible shows an expansive thin-walled cystic mass with thick septations.

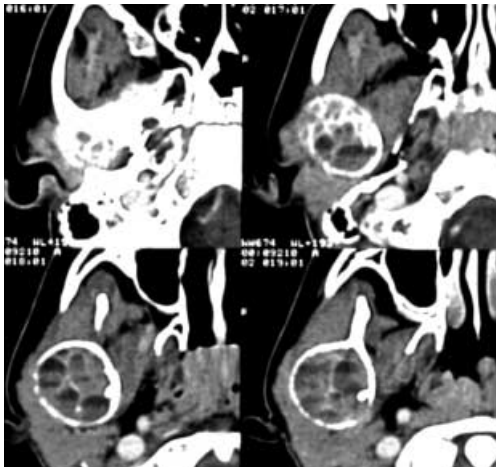

Figure 2. Aneurismal bone cyst. Contrast-enhanced CT shows expansive mass in the processus condylaris of the mandible with multiple fluid-fluid levels. The cortex is thinned but intact.

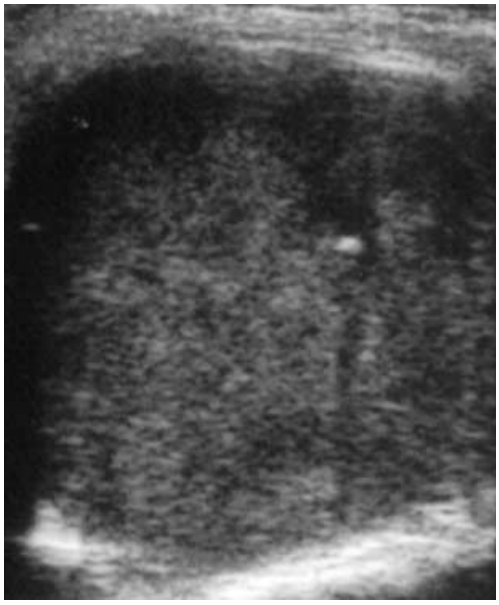

Figure 3. Central giant-cell granuloma. Longitudinal US scans of the processus condylaris of the mandible shows soft-tissue mass replacing bone.

Contrast-enhanced CT scans confirmed the presence of expanding soft-tissue mass replacing *processus condylaris of the mandible* with cortical expansion and thinning (Figure 4).

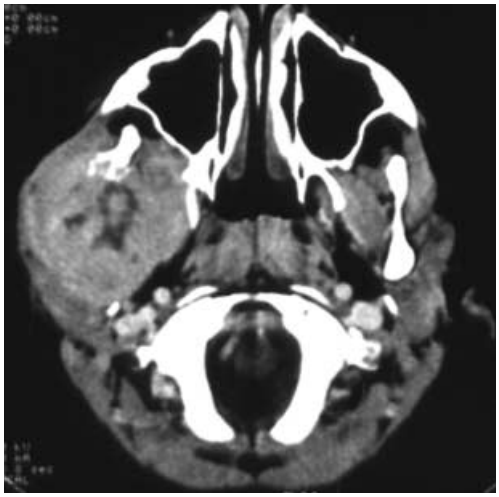

Figure 4. Central giant-cell granuloma. Contrast-enhanced CT scan confirms destruction of the processus condylaris of the mandible and associated soft-tissue mass replacing bone.

A biopsy of the lesion confirmed the typical histological appearance of a *CGCG* of the *processus condylaris of the mandible*. Although the parents of the child were familiar with the destructive nature of the tumour, they refused the operation, so the calcitonin treatment was commenced (100 IU or 0.5 mg of subcutaneous human calcitonin per day). Thirteen months after ceasing treatment there was no evidence of further growth. The lesion was filled with a soft, gritty bone.

Discussion

ABC is an erosive lesion of the bone, most commonly located in metaphysic of long bones and vertebral column in patients under the age of 30. Those that occur in jaws are rare, mostly involving the posterior part of mandible.[2,3] The cause of ABC is not fully settled. The aetiology is thought to be secondary to the increased venous pressure with haemorrhage that causes osteolysis. More often they are a reactive process, secondary to trauma or vascular lesion, caused by tumour or vascular malformation. Also ABC may represent a primary bone abnormality.[2]

Patients often have a history of pain and swelling, usually of less than six months duration.[2] CT scanning will define the lesion and is especially valuable for those lesions located in areas in which bony anatomy is complex, and which are not adequately evaluated by plain films.[5-7]

On the pathologic examination the underlying bone is replaced by cavities of various size filled with blood or/and proteinaceous material. ABC can heal spontaneously after curettage and bone grafting, surgical removal or after selective arterial embolization.[8-10] The removal of extensive mandibular and maxillary tumours is associated with the need of surgical tissue repair and prosthetic rehabilitation, and in young patients the surgical treatment must be followed by the orthodontic one.[11,12]

CGCG is a benign destructive bone lesion of the unknown ethiology. It represents 7% of benign lesions of joins, mostly involves parts of mandible and maxilla. It is of variable size and rate of progression, therefore some authors think that there is a spectrum of lesions that vary from the relatively benign CGCG of the jaws to the giant cell tumour of long bones, which may represent a low-grade sarcoma.[13]

The histological similarity of the CGCG to the »brown tumour« of hyperparathyroidism suggests the presence of an unidentified, circulating, PTH-like hormone. Microscopically, the lesion shows a collagenous stroma containing spindle cells and numerous multinucleated giant cells. An identical histological appearance can occur in the »brown tumour« of hyperparathyroidism, ABC and in cherubism. Due to the marked polymorphism a histological diagnosis of odontogenic tumours is often difficult, therefore, the correlation between clinician, radiologist and pathologist is especially important. A number of the lesions did stabilize or decrease in size and, if they were explored, a fibrous tissue scar was found in many cases.[14] However, it is generally thought that most CGCG are not reparative and are in fact destructive and will progress if not treated. The treatment of the CGCG lesion is generally surgical and consists of curettage or resection, which may be associated with the loss of teeth and, by younger patients, the loss of dental germ.[14] A resection is done by recurrent or more aggressive variants. Based on histological similarity between the CGCG and the »brown tumour« of hyperparathyroidism, Harris suggested that the CGCG might respond to calcitonin, even though there was no biochemical evidence of parathyroid disease.[15,16]

Although most commonly caused by parotitis or lymphadenitis, the swelling in the preauricular region in children may be a result of mandibular lesion (posterior area of the mandible) as it was a case in our patients. It is our opinion that, to establish an early diagnosis and begin with the treatment on time, an US examination of the preauricular swelling in all patients seems not only reasonable, but also necessary. A high-resolution US enables an accurate analysis of soft tissue and helps in the differential diagnosis. It also enables an accurate location of the lesion, which helps to avoid a wrong interpretation based on the clinical finding only. The CT-scan performed afterwards provides necessary information for the assessment of location, structure and size of the lesion. These lesions are often difficult to differentiate on the basis of their radiographic features alone.

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Transrectal and transperineal sonography in the diagnosis of hydradenitis suppurativa

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Background. *The aim of this paper is to present the application of transrectal and transperineal sonographies in the differential diagnosis of the hydradenitis suppurativa with the anal fistula.*
Patients and methods. *Transrectal and transperineal sonographies were performed in 8 patients with a clinical diagnosis of the anal fistula (6 patients) and the hydradenitis suppurativa (2 patients) in order to define precisely the relation of the inflammatory changes to the anal canal.*
Results. *In all patients the endosonography showed the preserved structures of the anal canal and the transperineal approach proved the superficial location of lesions.*
Conclusions. *Transrectal and transperineal sonographies are helpful in the differentiation between the hydradenitis purulenta and the anal fistula. The use of both methods enables a correct diagnosis.*

Key words: hidradenitis suppurativa - ultrasonography; rectal fistula

Introduction

The hydradenitis suppurativa (HS) or Verneuil disease is a chronic purulent inflammation of the skin and subcutaneous tissue. This entity affects apocrine glands, which are located in axillas, groins, around breasts and anus. Apocrine glands in these regions differ from glands situated in other regions of the body. They are usually located more deeply and are larger. According to the latest data the HS is genetically determined as an autosomal dominant disease, and also results from the elevated level of androgens.[1] Frequently the HS is misdiagnosed as an anal fistula. It is because the symptoms of the HS most frequently observed in the area of the anus or perineum include the inflammatory changes of the skin and subcutaneous tissue that, by the proctologic examination, very frequently resemble the anal fistula. The inflammation of the apocrine glands involves, however, superficial tissues and has no connection with the anal canal. Decisive examina-

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tions for a differential diagnosis are anoscopy, both transrectal and transperineal sonographies which confirm the superficial location. The treatment of the Verneuil disease is alike as for the anal fistula and involves the resection of the inflamed skin and subcutaneous tissue. If the area of the inflammation is very extensive, a few steps procedures are performed, and more than once, if necessary, a skin graft is desirable to cover the wound. Some use an ozone therapy or a local radiotherapy for recurrent inflammatory changes.

The aim of the study was to present the application of transrectal and transperineal sonographies in the differential diagnosis of the hydradenitis suppurativa with the anal fistula.

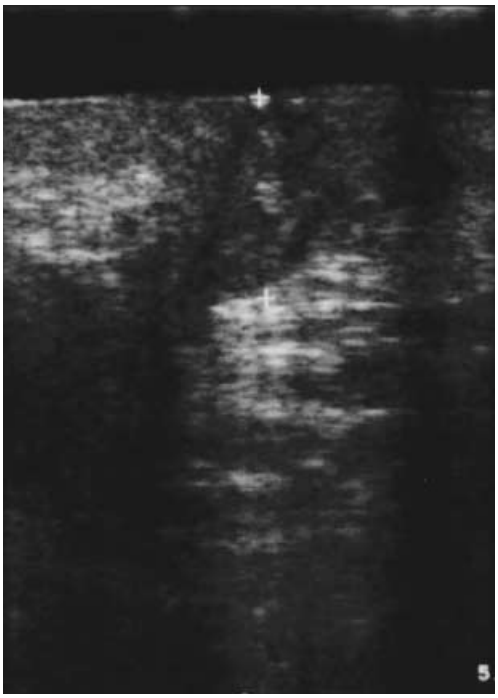

Figure 1. Superficial abscess in transperineal sonography.

Patients and methods

Eight patients (2 women and 6 men, aged between 27-62 years; mean age 54,5 years) with the clinical diagnosis of the anal fistula (6 patients) and the hydradenitis suppurativa (2 patient) were examined. All patients suffered from the recurrent purulent inflammation of the skin and subcutaneous tissue around the anus. They were all sent for a consultation to the proctologist. A proctologic examination together with a rectoscopy did not prove the relationship of these changes with the anal canal. To confirm this diagnosis transrectal and transperineal sonographies were also performed in 2 co-operating diagnostic departments. For this purpose Siemens Sonoline SI-450 with transrectal multiplane sector probe 7,5MHz (in 5 patients) and Bruel & Kjarer 3535 with 10MHz transducer (in 3 patients) were used, and a transperineal sonography was performed with the linear 7,5MHz probe. The patients were examined in the left lateral position. No preparation was required before the examination.

Results

In all patients superficial inflammatory changes of the mixed echogenicity, mostly hipoechoic, were visualised in the transperineal sonography. Tubular forms were representing superficial fistulas, round or oval represented superficial perianal abscesses (Figure 1) and uniform hipoechoic areas were seen in the areas of the inflamed skin and subcutaneous tissue (Figures 2a, 2b). A transperineal approach precisely defined the range of inflammation and correlated it with skin changes. The transrectal sonography was decisive in the precise assessment of the relation of these lesions to the anal canal. In all studied cases the preserved structures of the anal canal were shown (Figure 3). A transrectal approach was useful in 2 patients who

had relatively deep located abscesses and so it was difficult to define their relation to the anal canal. The final diagnosis was made after the confrontation of both approaches.

Discussion

Although the inflammation of the apocrini glands of the perianal area is not common its tendency to recur and involve the extensive area of skin causes a serious therapeutic problem. A prompt diagnosis is requisite for a successful treatment. As skin changes resemble the anal abscess or external openings of the anal fistula the HS is rarely recognised. An anal endosonography is currently one of the most widely used imaging techniques in the diagnosis of anal canal diseases.[2-9] A major role of the endosonography, as well as other imaging modalities, is to establish the relation of the fistula and the anal abscess to the anal sphincters. This simple and well tolerated examination allows in many cases for a precise and definitive diagnosis of the fistula and the abscess as well for the follow-up of these patients after the surgery. The accuracy of the anal endosonography in diagnostics of anal fistulas is up to 70%.[10.,11] The inflammation of the apocrini glands involves superficial tissues with the creation of small shallow abscesses and fistulas. A transperineal sonography is a satisfactory imaging examination to confirm this location. A transrectal sonography is rarely necessary in patients with the HS. Limitations of the endoanal sonography resulting from incomplete coupling of the probe to anal walls at the level of the anal verge are well known.[12] Air between the transducer and the anal wall produces artefacts, which obscure the image of the anal canal. In such cases a transperineal approach

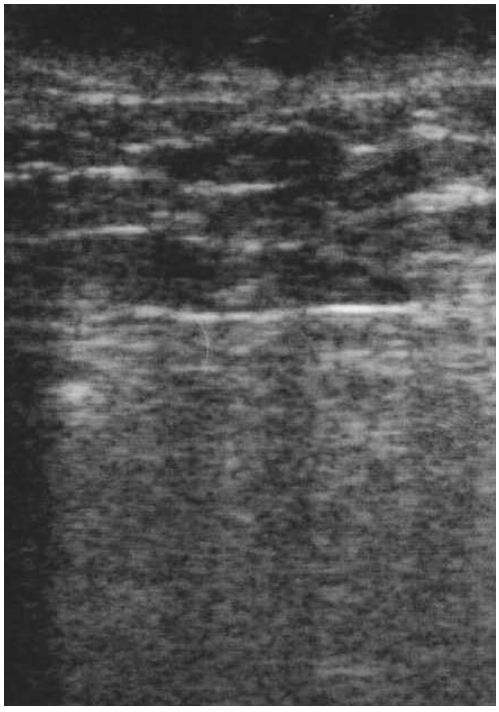

Figure 2a. Hipoechoic inflammed subcutaneous tissue in the right perianal area.

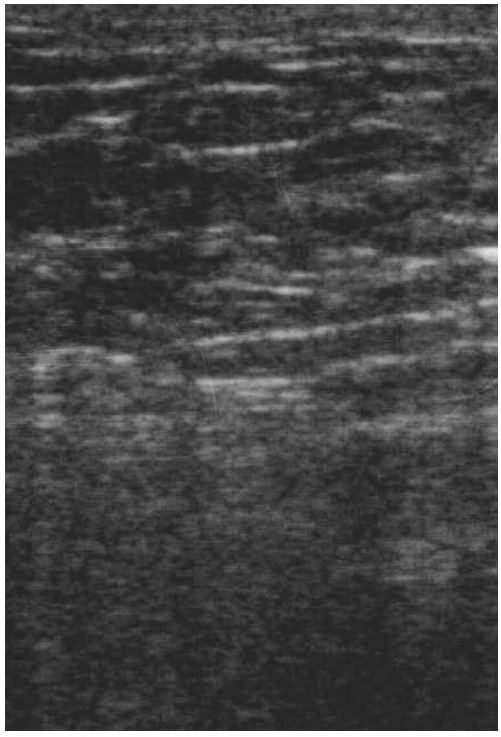

Figure 2b. Normal echogenicity on the left side.

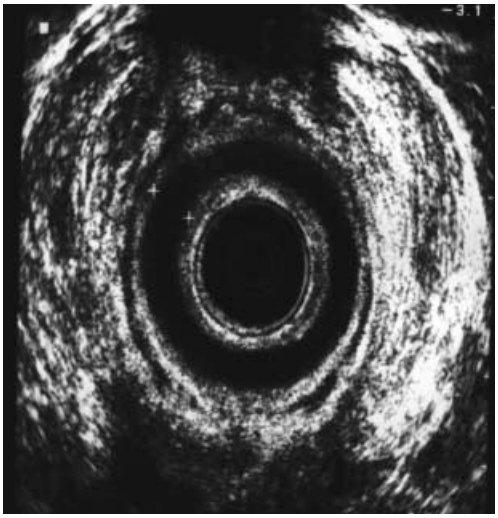

Figure 3. Preserved layered structure of the anal canal in transrectal sonography.

facilitates the diagnosis. Superficial abscesses, fistulas and the inflammation of the skin are better visualised using the linear probe with a large amount of gel for better coupling and stand-off (Figures 1,2,3).[12-16] The main indication for the endosonography is to exclude the communication of the perianal lesion with the anal canal. In 2 of the presented group of 8 patients it was difficult to define with the transperineal sonography if the very superficial abscess had the communication with the anal canal or not. The transrectal sonography showed a normal anal canal. Some reports proved a high accuracy of the transperineal approach not only in the visualisation of anal tumours and local recurrence, especially following the abdomino-perineal resection of rectal or anal tumours, but also in the diagnosis of anal abscesses and fistulas, and sphincters trauma involving a distal part of the anal canal. The quality of the image in the transperineal sonography is, however, not as high as in the transrectal endosonography; thereby its role is only additional. It may be very helpful in patients with the anal fistula or the abscess in whom, because of the strong pain, it will be impossible to introduce the probe into the anal canal. Under the control of the perineal probe, a drainage of the abscess may also be done, and a biopsy of any solid lesion or a differentiation between cyst, haematoma or abscess can be undertaken. In patients with the HP a transperineal approach is also very helpful. In 6 out of 8 presented cases with the initial diagnosis of the anal fistula superficial changes, typical for the HP were shown. In two others, deep abscesses were also visible; however, the reliable diagnosis was possible after the confrontation with the endosonography. Still, it must be stressed that in this presented entity a proctologic examination remains the most crucial for the diagnosis. Imaging techniques are also very helpful in the differential diagnosis, which is important in deciding on the choice of the surgical procedure.

Conclusions

Transrectal and transperineal sonography are helpful in differentiation Verneuil disease from anal fistula. The use of both these methods enables correct diagnosis.

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Pneumonia as a cause of death in patients with lung cancer

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Background. *Lung cancer is a very serious clinical problem in departments of pulmonary diseases. In many patients with lung cancer pneumonia is a secondary cause of death, which is caused not only by the progression of the disease but also by the applied treatment negatively influencing the immunity of human organism. Clinical and radiological symptoms of the infection can frequently suggest the progression of neoplastic disease. That is why in each case of deterioration of the state of patients with lung cancer the proper diagnosis of the cause should be endeavoured in order to implement the right therapeutic procedures.*

Patients and methods. *We have retrospectively evaluated 70 patients who died in the period between 1997and 1999 in our Department due to lung cancer. Both clinical and bacteriological analyses of deaths were performed and a particular interest in pneumonia as a cause of deat was taken.*

Results. *Pneumonia was diagnosed in 41 patients with lung cancer (58.5%) and Streptococcus pneumoniae was the main etiological factor of pulmonary infection. In patients with SCLC, the extent of inflammatory changes on chest X-ray and white blood cell count correlated negatively with the period of hospitalisation ($R = -0.6$ and $R = -0.54$; $p<0.05$, respectively).*

Conclusions. *Lung cancer was the main cause of death in patients died in the Department of Tuberculosis and Pulmonary Diseases, Medical University of Łódź. Pneumonia was diagnosed in 58.5 % as a secondary cause of death in lung cancer patients.*

Key words: lung neoplasms; pneumonia - mortality

Introduction

Lung cancer is the most common malignant tumour in men in Poland, with the morbidity index of about 50 in 100,000, and in women it is the fourth most common in respect of the frequency of occurrence (the morbidity index is about 8 in 100,000). All together every year about 20,000 new cases of the disease are recorded, and at the same time about 18,000 people die of lung cancer (in 1990 the number of deaths amounted to 19,301, and in 1998 to about 17,000 with the average death rate of 44.2).[1,2]

The main causes of death in patients with lung cancer are local progression of the disease, metastases to remote organs and the

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respiratory system infections.[3,4] Infections are the most frequent complications that break out by the treatment in this group of patients. The occurrence of infections is related to the immunological disorders connected with neoplasmatic disease, its location and progression as well to antineoplasmatic treatment. Among the factors favouring the respiratory system infections are mainly the ones, which are evoked by the presence of neoplasm in the respiratory system and its metastases to other organs.

The microorganisms responsible for infections in lung cancer patients may be bacteria, viruses, fungi and protozoa.[2,5] There have even been recorded some cases of infection caused by nemathelminthes. A patient with impaired immunity is primarily (by neoplasmatic disease) and secondarily (by the treatment) is exposed to the infection with pathogens and also with saprophytes (opportunistic infections).[6,7]

The aim of this research was a retrospective clinical and bacteriological analysis of deaths in lung cancer patients treated in the period between 1997 and 1999 in the Department of Tuberculosis and Pulmonary Diseases at the Medical University of Łódź, taking a particular interest in pneumonia as a cause of death.

Material and methods

The extent of the advancement of neoplasmatic disease was estimated on the basis of the physical examination, chest radiographs, chest and brain computed tomography, bronchofibroscopy and ultrasonographic examination of the abdominal cavity. Pneumonia was diagnosed on the basis of the following criteria: increased cough, purulent sputum, dyspnoea, increase in body temperature, rise in WBC (white blood cell count) and the occurrence of new infiltrates in chest radiographs.

A microbiological examination of the sputum was performed according to the Mulder-Lanyi method.[8,9] The sputum was collected into the Petri container in the morning, after washing of the mouth with water. This material was immediately sent to the Laboratory Department. Before the examination the sputum is 3-5 times washed by sterile 0.9% NaCl and the pus flakes are separated. Two preparations were made: Pappenheim for the cytological examination and Gram for the bacterioscopic one. Then the culture was performed and antibiotic sensitivity was denoted. The criteria of the infection covered: cytological examination, contents of eosinophils, Gram stain and culture.

Patient's characteristics

The total of 116 patients who died in the Department of Tuberculosis and Pulmonary Diseases at the Medical University of Łódź in the period between 1997 and 1999 were examined retrospectively. The primary cause of death in 70 of them (60%) was lung cancer (23 women, 47 men). As for the rest of patients the cause of death was COPD (25%), and a few others, such as tuberculosis, pulmonary fibrosis, pulmonary embolism, circulatory failure (15%). Fifty-one patients (73%) with lung tumour were diagnosed histologically: small cell lung cancer (SCLC) was diagnosed in 15 patients (6 women, 9 men), and non-small cell lung cancer (NSCLC) in 36 (5 women, 31 men). In 19 patients (12 women, 7 men) the type of neoplasm was not determined, and the diagnosis was given on the basis of the cytological examination of the sputum or bronchoscopic specimens (diagnosis: neoplasmatic cells). The average age of patients was 64.8 ± 11.8 years (SCLC: 62.8 ± 11.5; NSCLC: 63 ± 11.4). The extended disease (ED) was diagnosed in 13 (87%) patients with SCLC, the limited disease (LD) in 2 (13%). In the group with NSCLC the occurrence of metastases was detected in 12 patients (33%): clinical stage IV, and the rest of

patients were classified as stage III B. The mean disease period was 8.9 ± 4.6 months (median: 9 months) (SCLC: 8.6 ± 3.7 vs. NSCLC: 10.4 ± 4.8; p>0.05) and the average hospitalisation period was 7.8 ± 4.6 days (SCLC: 7.1 ± 4.3; NSCLC: 8.4 ± 4.8). All patients were smokers and the mean cumulated cigarette consumption was 40.9 ± 18.8 pack-years (SCLC: 37.0 ± 23.0; NSCLC: 41.6 ± 19.7).

The basic method of the treatment in patients with SCLC is chemotherapy. PE (cisplatin and ethoposide in six 3-day courses every 21 days) was the most often applied scheme among the examined patients (n=7). Not all the patients were given the full scheme (n=5) considering the lack of response or fairly large intensification of side effects. Alternatively the scheme CAV (cyclophosphamide, adriblastine and vincristine) was applied (n=2). In LD SCLC patients chemotherapy was supplemented with radiotherapy. The patients with NSCLC were covered by the palliative care. All patients received glucocorticoids (prednisone 20 mg/day).

Statistical analysis

The results were presented as an average value ± a standard deviation. Statistical differences were determined with the t-test or Kolmogorov-Smirnov test. Survival curves were constructed according to the Kaplan-Meier method and differences in the survival were compared with the log-rank test. Correlations were expressed as Pearson's or Spearman's coefficient depending on data distribution. A p value of < 0.05 was considered significant.

Results

Pneumonia was diagnosed as the secondary cause of death in 41 patients (58.5%). In the radiographs inflammatory changes occupy 3.4 ± 1.4 lung fields on average. In the blood examination no considerable changes were observed except the increased WBC (Table 1). There were no differences between measured routine panel blood parameters in SCLC and NSCLC patients.

The bacteriological diagnosis was given only in 6 patients (all with NSCLC) with pneumonia (8.5%) and Streptococcus was the most common evoking factor (Table 2).

All the patients with a diagnosed infection were subjected to the antibiotic therapy. The most frequently applied drugs were cephalosporins of II and III generation (n=15; 36.6%) and amoxicillin with clavulanic acid (n=6; 21.9%).

The autopsy was conducted in 4 patients (5.7%). In each case pneumonia was confirmed as a secondary cause of death.

Table 2. Bacteriological examination in patients with lung cancer and pneumonia

Etiologic agent	Number of patients	(%)
Streptococcus sp.	3	50
Proteus sp.	2	33
M. tuberculosis	1	17
Total	6	100

Table 1. Blood examination in patients with lung cancer and pneumonia

	Lung cancer (mean)	NSCLC	SCLC
Erythrocytes (10^6/μl)	4.4 ± 0.9	4.5 ± 0.9	3.9 ± 0.9
Hb (g/dl)	12.4 ± 2.6	12.5 ± 2.8	11.6 ± 2.8
Htc (%)	38.2 ± 7.8	38.5 ± 8.5	35.5 ± 8.3
MCHC (g/dl)	32.4 ± 0.9	32.4 ± 0.9	32.5 ± 1.1
Leucocytes (10^3/μl)	12.2 ± 7.0	13.1 ± 6.9	12.2 ± 8.4
Thrombocytes (10^3/μl)	294.5 ± 168.5	332.5 ± 180.0	236.8 ± 141.9

The survival median in the examined group was 9 months (Figure 1). For patients with SCLC it was 8 months, and with NSCLC 12 months ($p>0.05$). The correlation analysis of the examined parameters indicated that in the group of patients with SCLC the period of hospitalisation correlated negatively to WBC ($R = -0.54$; $p<0.05$) and the extent of inflammatory changes on radiological pictures ($R = -0.6$; $p<0.05$) (Figure 2). In the same group of patients the positive correlation between the extent of inflammatory changes on chest x-ray and WBC was found ($R = 0.68$; $p<0.05$).

The local progression of lung cancer (n=20) or the circulatory failure (n=9) were the cause of death in the rest of the patients.

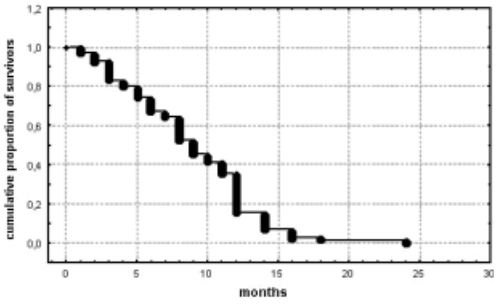

Figure 1. Survival in patients with lung cancer.

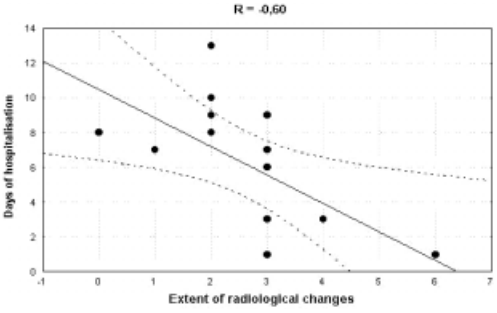

Figure 2. The negative correlation between the period of hospitalisation and the extent of inflammatory changes on chest x-ray ($R = -0.6$; $p<0.05$) in patients with SCLC.

Discussion

During the examined period in the Department of Tuberculosis and Pulmonary Diseases of the Medical University of Łódź the most common primary cause of death was the lung cancer (60%). It is estimated that about 75-80% of all patients with lung cancer are patients with the diagnosis of NSCLC, while 20-25% are patients with SCLC.[1,3] Similarly, in the examined group of patients the microcellular form of cancer was diagnosed in 21.4% of patients, while the non-microcellular form - in 51.4%. In the remaining patients (27.2%) the histopathological diagnosis was not made. The reason was often the short observation time of patients.

In the examined group of patients pneumonia was the main or accessory cause of death in 41 patients (58.5%). The conducted autopsy examinations in each case confirmed the clinical diagnosis. According to Remiszewski *et al.* in a group of patients with SCLC the infections of the respiratory system were the main cause of death only in 4.6% of patients, and the accessory cause in 9.1%.[6] In examinations conducted by Putinati *et al.* the frequency of occurrence of infections in lung cancer patients was estimated on the grounds of the results of the bacteriological examination of the broncho-alveolar lavage fluid (BALF), the presence of the infectious agent was indicated in 34.3% of patients. This result is probably underestimated because in some patients showing clinical symptoms of the respiratory system infections etiological agent was not discovered (sampling was conducted during the antibiotic therapy.[10] In Japanese examinations the group of patients with lung cancer was divided into three subgroups depending on the method of treatment and the frequency of the inferior respiratory tracts was estimated at 41.7-60.5%. Most often infections appeared in the group of patients receiving cytostatics and glucocorticoids.[11]

In patients with granulocytopoenia, apart from the typical for the respiratory system infections caused by alpha-haemolysing Streptococcus, Streptococcus from the D group, Staphylococcus aureus and epidermidis, Haemophilus influenzae, the important role is played by Gram-negative bacteria: Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter, Proteus. Subjects with the cell-mediated immunity disorders are exposed to infections caused by: Listeria monocytogenes, Salmonella, Mycobacterium, Nocardia asteroides and Legionella.[12,13]

The most frequently occurring virus infections include the ones caused by: Varicella-zoster, Herpes simplex, Cytomegalovirus and Ebstein-Barr virus.[13,14]

Other severe infections are the ones caused by fungi: Pneumocystis carinii, Cryptococcus neoformans, Aspergillus fumigatus, Candida albicans, Candida krusei, Histoplasma capsulatum, Candida glabrata, protozoa (Toxoplasma gondii). Infections caused by Strongyloides stercoralis were also observed.[7,15-18]

The conducted bacteriological examinations showed that the etiological agents of pneumonia in the examined group were bacteria of Streptococcus and Proteus species as well as Mycobacterium tuberculosis. Putinati *et al.* indicated Gram-negative rods as the most frequent cause of infections (most often Haemophilus sp.) - 45.2%, Gram-positive cocci (most often Staphylococcus aureus) - 33.3%, Pneumocystis carinii and Chlamydia trachomatis - 16.7% as well as Gram-negative cocci - 4.8%.[8] In the Japanese examinations cited before cases of pneumonia were caused by Gram-positive bacteria in 38.4%, Gram-negative bacteria in 30.8%, and mixed bacterial flora in 30.8%.[11] Remiszewski *et al.* showed that the most frequent etiological agents of the infections causing death of patients with lung cancer were Gram-negative bacteria (Klebsiella sp., Pseudomonas sp., Escherichia coli). Gram-positive bacteria (Staphylococcus sp., Streptococcus sp.) were isolated more sparsely. In some patients infections were caused by fungi: Aspergillus sp., Candida sp., Pneumocystis carinii and Mycobacterium tuberculosis.[2,5,6,15] It is difficult to compare these data with our results because of small number of bacteriological confirmations of the pulmonary infection (8.5%).

Due to the limited accessibility of microbiological tests and the possibility of rapid outcome of the infection in patients with lung cancer the empirical treatment is recommended.[19] Patients with neutropoenia below 500/μL are conventionally treated with aminoglycoside and β-lactamic antibiotic (amoxicillin + claevulanic acid or cephalosporins of II/III generation). In case of leucopoenia above 500/μl aminoglycoside and cephalosporin of III generation or cephalosporin of III generation and macrolid are administered. In patients with neutropoenia and fever cephalosporin of III generation and clindamycin are applied. In the lack of results of this treatment after 5 days a different etiology must be considered. In case of pneumonia caused by Pneumocystis carinii (PCP) trimetoprim-sulfametoxasol is usually applied.[13,18] In cases of infections caused by fungi patients are treated with amphotericin B.[2,7,20,21] In the examined group cephalosporins of II/III generation, amoxicillin with claevulanic acid and aminoglycosides were most frequently applied.

Severe pulmonary infections in lung cancer patients may develop due to local or systemic immunological disorders. Systemic immunological disturbances occur relatively early in patients with lung cancer. Irregularities concern mainly the cellular type of immunity.[6,22] What is advantageous to infections is also permeability disorder of bronchus caused by helophytic or intramural increase of the neoplasm or by the pressure to a bronchus wall caused by the mass of the tumour or enlarged lymph nodes. These phe-

nomena are intensified by the impaired cough reflex which may take place against the background of applied therapy (narcotics, psychotropic) or as a result of neoplasmatic metastases to brain.[23] Moreover, metastases to bone marrow may lead to leucopoenia and anaemia.[2,6,24] It seems that in our patients the main causes of pneumonia were atelectasis and dysfunction of phagocytes and lymphocytes (with normal or increased WBC), especially in NSCLC.

Another group of factors predisposing to the occurrence of the respiratory system infection includes those connected with the radical and palliative treatment for lung cancer. Most of drugs applied in the antineoplasmatic therapy have a suppressive effect on the function of the immune system. Alkalising drugs, antimethabolites of purines, pirimidines and folic acid produce the stronger immunosuppressive effect.[22,25] Almost all cytostatics create disorders of proliferation and function of granulocytes with a temporary shortage of these cells in the peripheral blood. In SCLC group of patients 60% received chemotherapy with cisplatin, etoposide or cyclophosphamide, adriblastine and vincristine and all of patients were treated with glicocorticosteroids. The risk of the infection increases considerably in patients whose number of neutrophils does not exceed 500/μl and is especially high in the case of neutropoenia below 100/μl.[10,25] Glucocorticoids are often used as supportive drugs in lung cancer patients. By the suppressive influence on the cellular immunity they contribute to the increase of susceptibility to infections.[12]

The syndrome produced by radiotherapy depends on the size of irradiated area and the amount of a total dose. Developing inflammatory changes in lungs may be responsible for the occurrence of respiratory failure and the patients' death, especially with this state being often complicated by the respiratory system infection.[2,3,26]

It is estimated that over 80% of patients do not survive the first year since the diagnosis, and only few per cent survive 5 years.[1,10] Similarly in the examined group the median of the patients' survival was 9 months (NSCLC: 12 months; SCLC: 8 months). Our results indicated additionally that the high intensity of pulmonary inflammation measured by WBC and the extent of radiological changes are connected with a poor prognosis and short period of hospitalisation. This was confirmed by our previous studies. The negative correlation between the serum concentration of lipid hydroperoxides and radiological regression was observed in patients with pneumonia after 14-days therapy.[27] Moreover, in patients with tuberculosis, the serum concentration of other inflammatory indicators such as conjugated dienes, thiobarbituric acid-reactive substances,[28] soluble tumour necrosis factor receptor I, and intercellular adhesion molecule-1 were significantly higher in the radiologically advanced disease.[29]

Conclusions

(1) Lung cancer was the main cause of death among our patients; (2) Pneumonia was diagnosed in 58.5% as a secondary cause of death in lung cancer patients; (3) In patients with SCLC, the extent of inflammatory changes on chest X-ray and WBC correlated negatively with the period of hospitalisation.

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Radiotherapy for stage IAE non-Hodgkin's lymphoma of the testicle - a case report

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Background. *The aim of this report is to present the irradiation technique applied to a patient with primary testicular non-Hodgkin's (NHL) lymphoma stage IEA, histologically CD20 positive NHL - diffuse follicular center cell (FCC) lymphoma grade III. Since primary NHLs of the testis are rather rare, no uniform radiotherapy approach to their treatment has been developed to date. Testicular NHLs are relatively often of aggressive biological characteristics, so that the disease relapse is not uncommon even in patients in an early stage of the disease (stage I and II), who received seemingly optimal therapy (orchiectomy of the diseased testicle, polychemotherapy and irradiation).*

Case report. *In this report the applied radiation treatment field is shown. The disease was diagnosed in June 2001 after the inguinal orchiectomy. Afterwards, the patient received 6 courses of polychemotherapy (CHOP) plus intrathecal methotrexate therapy. The irradiation was conducted with one direct 6 megavolt (MV) energy photon beam. The irradiation field encompassed the contralateral testicle (scrotum) and inguino-femoral lymph nodes. The radiotherapy dose was 30 Gy applied in 15 fractions calculated at the depth of 4 cm. The radiotherapy finished in December 2001. The patient has regular check-ups (last in May 2003) and has been in remission since then.*

Conclusions. *Relapse sites are quite often extranodal, not in the regional lymph nodes. Therefore, considering the radiation treatment fields there are no definitive recommendations.*

Key words: testicular neoplasms; lymphoma, non-hodgkin

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Introduction

Primary lymphoma of the testis is a rather rare disease. It accounts for around 1% of all NHL's, 2% of extranodal lymphoma and less than 10% of all testicular neoplasms. However, in men over 60, it is the most common malignancy of the testis. The prognosis of testicular lymphoma is relatively poor com-

pared to other nodal and extranodal lymphomas. Median survival is 12 to 24 months.[1-3]

Because this entity is relatively rare, much of the literature includes reports on a limited number of patients (usually between 10 to 30) collected over a span of many years.[4-17] Accordingly, one can find differences in both lymphoma classifications and treatment approaches. Recently, two publications including a much larger number of patients have also appeared due to the multicentric or international nature of data collection and study.[15,17] Due to their relatively larger number of patients, these recent publications allow us to better define the specific clinical features at presentation, prognostically important clinical variables, a response to therapy, and patterns of failure.

Most of primary testicular lymphomas are of B-cell origin, and overall diffuse large B-cell lymphomas as well as diffuse small noncleaved cell lymphoma appear to be the most common type. Follicular lymphomas and other histologic subtypes are less frequently represented.[1-3] Inguinal orchiectomy is universally recommended as an initial therapy for patients with localized disease. Although the long-term disease-free survival has been described after the orchiectomy alone, the vast majority of the patients relapse, so this cannot be considered an adequate therapy, not even for patients with IE disease. Furthermore, relapse rates exceeding 50% have been observed in the majority of reports in which the adjuvant radiotherapy (RT) was used following the orchiectomy. Relapses often occur in extranodal sites, such as in the central nervous system (CNS), Waldeyer's ring, skin and lung. In field failures were reported in patients who received adjuvant locoregional radiation at doses lower than 30 to 35 Gy. Such clinical course suggests that testicular NHL is usually a systemic disease, even when it initially presents as a localized disease. Accordingly, combined chemotherapy and radiation therapy have been the accepted treatment modality for stage IE and IIE aggressive nodal lymphomas. The chemotherapy is usually doxorubicin based (for example, CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone) accompanied with concomitant CNS prophylaxis (4-6 injection of methotrexate intrathecally). The radiotherapy, if any, is usually applied in a form of involved-field, encompassing the contralateral testis (scrotum) or scrotal, iliac and possibly para-aortic regions. A routine use of irradiation to the paraaortic lymphnodes is not recommended because of the unpredictable metastatic pathway of the primary NHL lymphomas. The irradiation of the contralateral testis is with a prophylactic intention since the relapse rate in case of nonirradiation, is approximately 8% to 35%.[1-3] On the other hand, there are also reports where the irradiation of the contralateral testis was either not performed[5,7,9,11] or performed only in a portion of patients reported.[4,12,15,17]

Regarding radiotherapy, these reports surprisingly include very few details about the target volume and techniques.[4-17] Concerning the radiation dose, they regularly mention the total dose. The target volume and irradiation technique is usually not precisely described. In a sentence or two it is mentioned that the involved field or involved-region irradiation was administered, or that scrotum and pelvic (iliac) lymphnodes ± paraaortic lymphnodes were irradiated. Therefore, we present the irradiation treatment we applied to a patient with stage IEA primary testicular NHL lymphoma.

Case report

The presented patient was born in 1937. Due to the enlargement of the left testis he was examined at the Department of Urology, Clinical Hospital »Merkur«, Zagreb, Croatia. A diagnostic examination, which included al-

so the computerized tomography (CT) of the abdomen and pelvis, did not reveal or indicate a disease spreadout outside of the left testicule. In June 2001, the patient underwent the left inguinal orchiectomy. The pathologic diagnosis was »CD20 positive NHL - diffuse follicular center cell (FCC) lymphoma grade III« (Diffuse large B-cell lymphoma according to the revised European-American classification of lymphoid neoplasms (REAL) - World Health Organization (WHO) classification).[3]

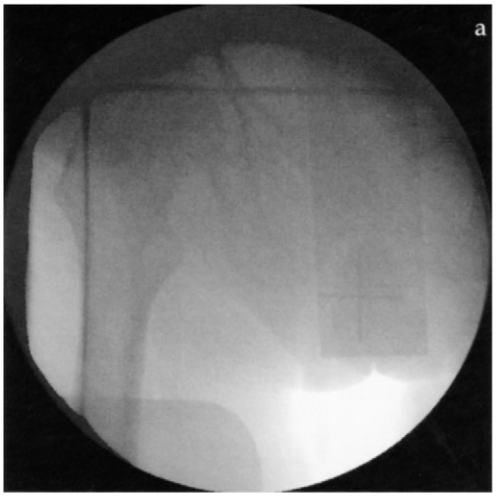
The patient was thereafter referred to a hematologist at another hospital (Department of Hematology, Clinical Hospital »Dubrava«, Zagreb). There he underwent an additional extended staging procedure that also included CT of the head and neck, thorax and abdomen and pelvis again as well as the bone marrow examination. These examinations did not show any evidence of the disseminated disease and/or regional lymph node involvement. Accordingly, the patient was diagnosed with primary NHL of the testicle, stage IAE. Moreover, according to the International Prognostic Index (IPI), he could be classified among low risk patients. His age was a risk factor (>60), while other four parameters did not indicate the elevated risk (serum lactate dehydrogenase was within normal limits, performance status - ECOG score = 0, stage of the disease I, one extranodal site involved).[3,18]

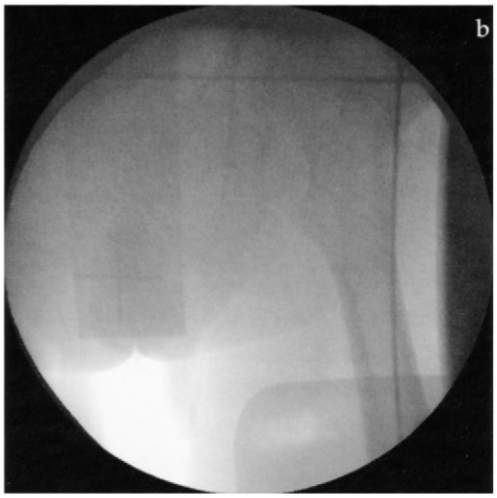
He was treated thereafter with six cycles of CHOP polychemotherapy (cyclophosphamide, 750 mg/m^2 i.v. on day 1; doxorubicin, 50 mg/m^2 i.v. on day 1; vincristine, 1,4 mg/m^2 i.v. on day 1; prednisone, 40 mg/m^2 p.o. on days 1 to 5) and intrathecally with methotrexate (15 mg on the first day of each CHOP chemotherapy cycle). Cycles of CHOP polychemotherapy were administered at 3-week intervals.

When the patient completed the chemotherapy treatment he had a control examination. No signs which could indicate the disease relapse or the development of distant metastasis were found. After that, he was referred to radiation oncologists at the University Hospital for Tumors in Zagreb for the further radiotherapy treatment. Taking into account patient's previous treatments, the possible clinical course of the disease and the patient's overall good condition (ECOG score 0), it was decided that he should receive the consolidation radiotherapy, to be applied to the contralateral testis (scrotum) and the neighboring inguino-femoral lymph nodes and subcutaneous lymph-vessels (»involved-field«). The total tumor dose was 30 Gy in 15 fractions.[1,2,19]

Radiation details

Since the scrotum and the inguino-femoral lymphnodes are located superficially, the radiotherapy was performed by a single »direct« beam. Moreover, the region was encompassed by a single radiation field. The radiation was planned as nonisocentrical, using a single 6 MV photon beam from the linear accelerator, having a focus to skin distance (FSD) of 100 cm, with the gantry angle of 0 degree (antero-posterior direction), respectively. The radiation field was determined during the simulation process by using a treatment-planning simulator. The patient was placed supine on the simulator table with his arms crossed over his chest (Figure 1). Consequently, for the radiotherapy the patient was always identically positioned. By means of simulator x-rays, the radiation field was tailored so to encompass the scrotum and inguino-femoral lymph nodes (Figure 1). The size of the treatment radiation field was 25 x 17.5 cm (Figure 1). After the appropriate subtractions of the shielded surfaces, the size of the radiation field approximated 18 x 18 cm. At the central axis the patient's antero-posterior diameter was 21.5 cm. The total tumor dose of 30 Gy, or single irradiation fractions of 2 Gy were calculated at the 4 cm depth. The isodose plan is shown in Figure 2. To obtain a comparably homogenous dose





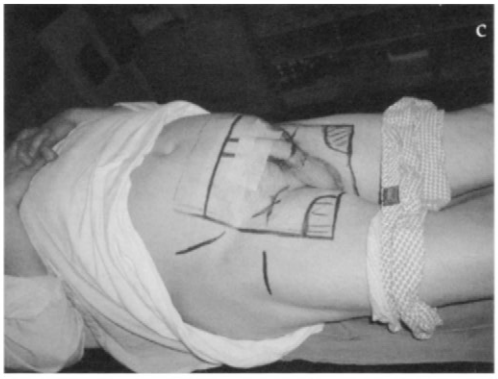


Figure 1. Presentation of the irradiation field. Figures 1a and 1b show different parts of the same radiation field, i.e., x-ray images taken on a simulator during radiotherapy planning. Irradiation of the contralateral testicle, scrotum and of inguino-femoral lymph nodes is achieved. The position of shielding blocks for the penis and lateral parts of thighs can be observed. Figure 1c shows the radiation field on the patient body. Plexiglass located shielding blocks enable protection of the penis (fixed by an adhesive plaster tape) and lateral part of thighs.

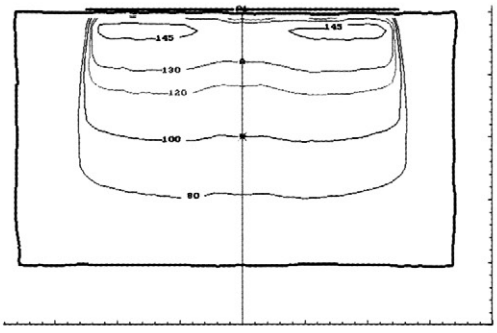


Figure 2. Two-dimensional presentation of the dose distribution ratio by depth delivered by 6 MV photons. (isodose curves, i.e., isodose plan). Centimeter scale is shown on the left and at the bottom. Point »A« in the isodose plan denotes the depth of 4 cm - a dose of 2 Gy per fraction.

distribution within the depth of the first 4 cm, tissue bolus in equivalency of 6 mm of water is used during the irradiation. Finally, after having all calculations done, reviewed and approved, irradiation was carried out. The radiotherapy was conducted in December 2001.

Discussion

This case report is aimed at pointing out the difficulty a radiation oncologist may encounter in planning the radiotherapy for a disease with primary tumors being surgically removed and a propensity for primarily distant metastasis, the disease with no strict recommendations for the radiotherapy due to its

rarity. For example, in the publication from Zucca *et al*[17] which includes 373 patients, the authors admit that among the patients receiving radiotherapy (n=196, as primary or as combined with chemotherapy) there is a wide range of radiotherapy doses (from 18 to 50 Gy) and fields (from only scrotal to a variety of extended fields with or without inclusion of the contralateral testis).

When considering the total tumor dose and the target volume we took into account the possible pattern of relapse, patient's stage of the disease, previous treatments, and his overall good condition. Moreover, the radiosensitivity of the testicular NHL cells, possible existence of microscopic residual NHL cells in both the contralateral testis and inguino-femoral lymph nodes, normal tissue tolerance and possible side effects of irradiation to normal tissues were also taken into account.[1-3,19] The irradiation could be performed also by a photon beam from a cobalt-60 machine, but due to the fact that the patient was obese with a substantial slope difference between the upper and lower field portions, 6 MV photons were given advantage. We have also been considering the usage of 20 MeV electrons, but the field size was a problem, as well as the patient's contour slope and especially the construction of a penis-shielding block. Megavolt electron beams show the advantage in the deeper body structures receiving much less of the radiation energy. If the irradiation has to be applied only to the scrotum, then the megavolt electrons are satisfactory. At the total tumor dose of 30 Gy in 15 fractions one does not expect an intensive painful skin reaction (irradiation dermatitis) of the scrotum by using megavolt electrons.

The radiation therapy was well tolerated by the patient. The standard routine control examination was 6 weeks after the irradiation had been completed. The patient was well and felt well in the postirradiation period. No skin reaction (irradiation dermatitis) was observed. At examination, his locoregional status was in order. Standard laboratory test results were also normal. Since then, the patient has regular check-ups every three to four months (last in May 2003.) and is in remission since then.

Considering the treatment strategy for non-Hodgkin's lymphoma (NHL) it is largely determined by the histologic sub-type, stage at diagnosis and by the patient's overall condition.[1-3,20] The treatment of localized (stages I, IE, non-bulky II and IIE) aggressive histologies of non-Hodgkin's lymphoma has been evolving over the past 20 years. These diseases could be locally controlled with the radiotherapy, but systemic relapses and deaths are common. Cure rates for the intermediate- and high-grade localized NHL improved dramatically with the addition of doxorubicin-containing chemotherapy. In the 1990s, two large randomized, prospective trials demonstrate that initial chemotherapy followed by the radiation therapy (combined modality therapy) gives the best results; so, such combined treatment might be considered as the best available current treatment strategy.[18,21]

Within the group of aggressive NHLs the prognosis of testicular lymphoma is relatively poor compared to other nodal and extranodal aggressive lymphomas[1-3,8,15,17,22]. The surgery, i.e. orchiectomy, has an important role in the diagnosis, but its usefulness, unless the disease is really limited to the testis, is restricted. As mentioned, available data suggest that in the majority of stage IE patients systemic occult metastases are already present. Accordingly, the radiotherapy usually has also a limited role. The goal of RT in the treatment of localized aggressive NHL is to deliver an adequate dose to the disease site and margin. The radiation is generally given after the initial chemotherapy treatment. Factors determining the dose of radiation, aside from normal tissue tolerance, include bulk of disease and performance status. In case of testicular lymphoma, the affected organ has usu-

ally been already removed by orchiectomy. Due to an unpredictable metastatic pattern of the testicular NHL, the question is what to irradiate. The irradiation is applied on the assumption that the probable site of the initial relapse will be in the pelvic or para-aortic lymph nodes or in the contralateral testis. Distant extranodal failures, especially in the CNS, remain a major problem, even in patients who receive a full course of doxorubicin-based chemotherapy accompanied with the intrathecal CNS prophylaxis with methotrexate alone or combined with cytarabine.[16,17] In the cases of CNS relapses it may be important to distinguish intraparenchymal failures from the lepromeningeal ones since for the prevention of intraparenchymal failures more effective CNS prophylaxis, such as low-dose whole-brain irradiation or high-dose methotrexate must be prospectively explored.[11,16] The recent multicentric prospective studies with a relatively high number of patients indicate that, because of the poor prognosis, an aggressive treatment approach, if possible, is warranted.[16,17] For example, the results from the Zucca's study[17] indicate that among the prognostic factors that were statistically significant at the multivariate analysis, IPI, B symptoms, anthracycline-containing chemotherapy, and prophylactic scrotal irradiation retained statistical significance with the overall survival (OS), cause-specific survival and progression-free survival. Patients receiving radiotherapy have a significantly longer OS, but most of them have a favorable IPI score. Among patients receiving radiotherapy locoregional to the primary testicular site of involvement, the OS was longer for those receiving an irradiation dose of at least 30 Gy. On the other hand, testicular lymphoma is predominantly a disease of older men who often have limited ability to tolerate aggressive treatment. The rarity of the disease makes randomized trials virtually impossible. Hence, an international collaboration is crucial to properly address the management of testicular lymphoma. The improved understanding of the genetic and molecular characteristics of testicular lymphoma may help identify patients at risk of CNS failure and apply a patient-tailored treatment in the future.[15,17]

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case report

Long-term disease-free interval after irradiation for locally advanced lung cancer

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Background. *The purpose of the report is to describe a patient with the lung cancer who had long-term disease-free interval after the irradiation therapy.*
Case report. *The patient was a 58-year-old woman with large cell lung carcinoma with neck lymph node metastasis, which was treated with radical radiotherapy. Within a 9-year disease-free interval, the patient developed loco-regional recurrence and distant metastases.*
Conclusions. *Despite a long-term disease-free interval, non-small cell lung cancer represents a life-long threat to some patients and requires constant vigilance by medical practitioners.*

Key words: lung neoplasms - radiotherapy; carcinoma, non-small-cell lung; disease free survival

Introduction

Locally advanced non-small cell carcinoma of the lung is one of the good candidates for irradiation therapy because of its anatomical location. Despite radical radiation therapy, local recurrence is observed in 20 - 60 % of patients with non-small cell lung cancer and the majority of all recurrences develop within 2 years after radiation therapy.[1-3]

We report a case of recurrence within a 9-year disease-free interval of the first course of irradiation therapy.

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Case report

In February 1991, a 58-year-old woman was admitted to our hospital with cervical lymph node swelling which she noticed three months prior to the presentation. She was basically healthy without significant past medical history. Her physical examination revealed cervical lymph node adenopathy on the right. Bulkily swollen right mediastinal lymph nodes with a tumour of the right upper lobe, which was adjacent to the swollen lymph nodes, were observed on chest X-ray and CT scan on admission (Figure 1). Biopsy from the cervical lymph node revealed metastatic large cell carcinoma of the lung. A brain MRI and an ultrasound echogram of the abdomen and a bone scintigram revealed no metastasis, therefore we treated her as patients with locally advanced disease in spite of there were proven metastases in the cervi-

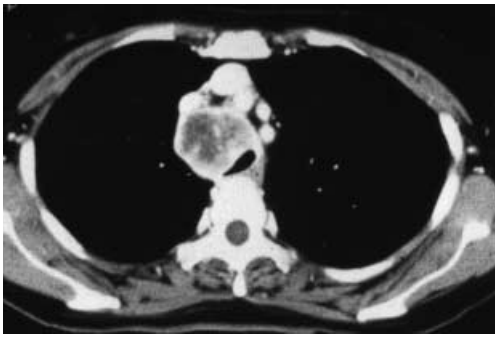

Figure 1. Chest CT scan on admission. Bulkily swollen right mediastinal lymph nodes with a tumour of the right upper lobe, which was adjacent to the swollen mediastinal lymph nodes, were observed.

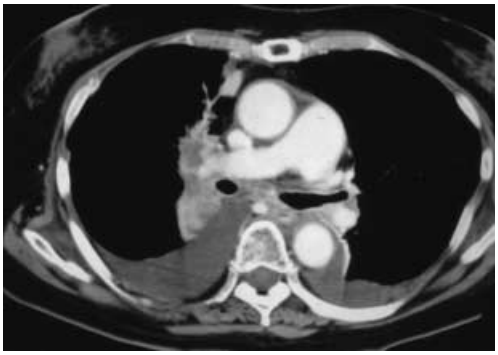

Figure 2. Chest CT scan on second admission. Loco-regional recurrence of the right upper lobe of the lung was observed.

cal lymph nodes. However, we clinically diagnosed this patient as large cell carcinoma of the lung of right upper lobe; clinical T3N2M1, stage IV. Thereafter, she received external radiation therapy to the primary lesion, mediastinal and supraclavicular lymph nodes and right cervical lymph nodes with a total dose of 60 Gy in 30 fractions over 47 days. The response was evaluated as partial response; the patient then received one course of chemotherapy consisted of cisplatin, vindesin, and ifosphamide. The patient was discharged from the hospital and followed up regularly. She was free of any signs of recurrence until February 2001, when she developed dry cough and dysarthria.

Chest CT scan revealed loco-regional recurrence of the right upper lobe of the lung (Figure 2), and brain MRI shown multiple nodular metastases to the cerebrum (Figure 3). We also observed multiple uptakes on bone scintigram (Figure 4). The patient did not want to receive additional intensive therapy and she died of the disease one month after the diagnosis of loco-regional recurrence and distant metastasis. Post-mortem examination was not permitted.

Discussion

Radiotherapy is one the choice of treatment for locally advanced non-small cell lung cancer owing to an anatomical restriction. Despite radical radiotherapy, a relatively high incidence of loco-regional recurrences has been observed.[1-3] Although the majority of all loco-regional recurrences develop outside or at the margin of the treatment portal within 2 years after radiation therapy, some recurrences have been observed after a long latent period.[4-7] Most of the distant metastases also

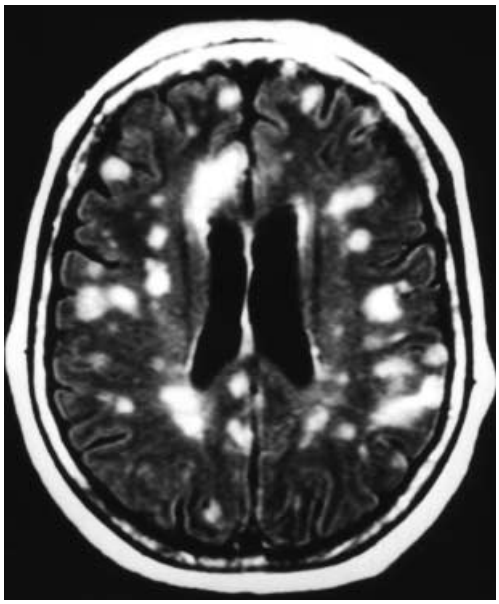

Figure 3. Brain MRI on second admission. Multiple, nodular metastasis to the cerebrum were observed.

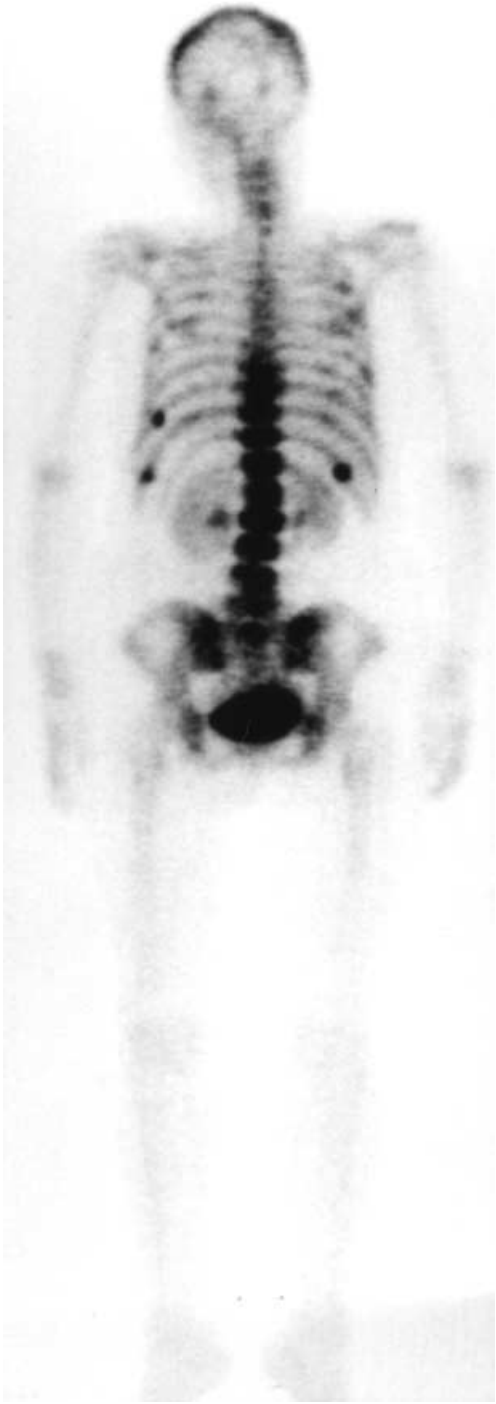

Figure 4. Bone scintigram on second admission. Multiple uptakes were observed on the scintigram.

occur within 2 years after treatment and the common sites of distant metastases are the bones and/or lungs.[3] Our patient developed recurrence inside the irradiation field and distant metastases within a 9-year disease-free interval of the first course of radiation therapy for the primary lesion and cervical lymph node metastasis.

Many recent investigators have recommended chemotherapy with taxan for recurrent non-small cell carcinoma.[8,9] Very recently, Gefitinib, an oral selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, has been reported to be a safe agent, although some toxic effects, such as interstitial pneumonia, diarrhea and skin rash have been recognized.[10-12] But our patient did not want to receive any additional intensive treatment. Moreover, the patient's condition got worse very rapidly and she died of the disease only one month after the diagnosis of recurrence.

A general belief in the treatment of cancers has it that a cure is present if the disease-free interval is longer than five years. This concept may apply to the majority of cases of lung cancer, but rare cases do recur after many years of disease-free survival. Most of these patients who had long-term of disease-free interval were those with lung adenocarcinoma.[4-7] Therefore, a recurrence of large cell carcinoma of the lung within 9 years after irradiation is almost unique. Although the patient had developed loco-regional recurrence and distant metastases, we had some hope for her additional long-term survival, because the patient had a long disease-free interval from the initial therapy to the recurrences and because there has been no deterioration in her performance status for more than 9 years after the completion of the radiation therapy. This observation suggests either a long period of dormancy of residual large cell carcinoma cells prior to re-initiation of proliferative activity or the presence of a more slowly growing population of residual cells.

Certain clues of mechanism of the late recurrence might have existed in the clinocopathological information; but, at present, we are not able to detect the clues. Whatever mechanism was involved, it is clear that radical radiation therapy did not provide certain cure in our patient. Despite a long-term disease-free interval, large cell carcinoma of the lung represents a life-long threat to some patients, and it requires constant vigilance by medical practitioners.

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review

The role of cyclooxygenase-2 in the malignant tissue and possible applicability of cyclooxygenase-2 inhibitors in the therapy of cancer

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Cyclooxygenase-2 (COX-2), an inducible prostaglandin (PG) synthase, is elevated in many types of malignant and pre-malignant tissues. This enzyme is localized in neoplastic (epithelial) cells, microvascular endothelial cells, and stromal fibroblasts. Through the released PG it enhances carcinogenesis with increasing angiogenesis, inhibiting apoptosis, activating matrix metalloproteinases, suppressing of cell mediated antitumor immune response and protection against damage by cytotoxic agents. Evidences from in vitro studies, studies on animal models as well as first clinical outcomes suggest that the inhibition of COX-2 may suppress carcinogenesis by affecting a number of pathways: inhibiting angiogenesis, invasiveness of tumors and promoting apoptosis. References forecast that COX-2 inhibitors, mostly COX-2 selective inhibitors, may get a role in the therapy of cancer as an adjuvant therapy or as an co-chemotherapeutic agent. The purpose of the present article is to summarize the most important facts about the role of COX-2 in the malignant tissue and discuss possible ways for potential therapeutic place of COX-2 inhibitors in clinical practice.

Key words: neoplasms - drug therapy - physiology; cyclooxygenase inhibitors; apoptosis

About cyclooxygenase

Cyclooxygenase (COX) enzyme is a prostaglandin (PG) H synthase that catalyzes the rate limiting step in the production of PG and tromboxanes. It mediates the insertion of molecular oxygen into arachidonic acid that is liberated from membrane glycerophospholipids and forms unstable intermediate PGG2 that is rapidly converted to PGH2 by the peroxidase activity of COX. Specific isomerases then convert PGH2 into biologically active PGs, such as PGF2 alpha, PGE2, PGD2, PGI2, and thromboxane (TX) A2. PGs have important function in almost every organ system; they regulate diverse physiological processes, such as immunity, reproduction, maintenance of vascular integrity and tone, nerve growth and development and bone metabolism. PGs act as autocrine and paracrine mediators to signal changes within the immediate environment.[1,2]

There are two isoforms of COX: COX-1 and COX-2. They are encoded by different

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genes and express cell-specific regulation. COX-1 is constitutively expressed in most mammalian tissues and is responsible for normal kidney and platelet function and for the maintenance of gastrointestinal mucosa.[3] On the other hand, COX-2 is not detected in most of normal tissues. It is induced by mitogenic and inflammatory stimuli, which results in an enhanced synthesis of PGs in neoplastic and inflamed tissues.[4]

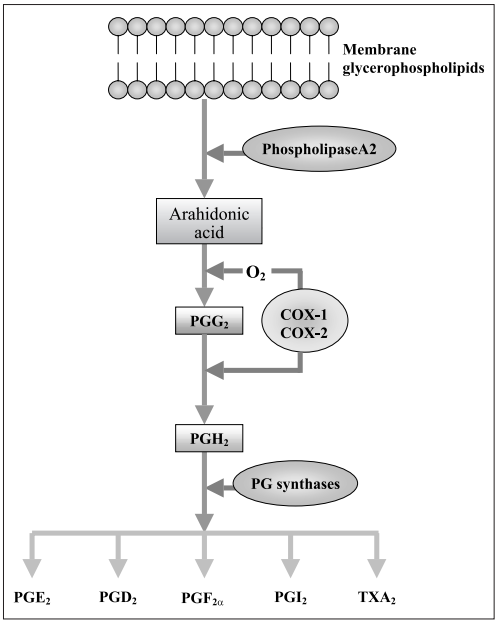

Figure 1. Cyclooxygenase enzymes in prostaglandin synthesis.

COX-2 is overexpressed in several premalignant and malignant conditions

There are growing evidences that COX-2 is commonly overexpressed in malignant tissue. Eberhart *et al.*[5] first noted that COX-2 is upgraded in colorectal cancer. Till today, COX-2 overexpression was found in the colon adenoma and adenocarcinoma, stomac metaplasia and adenocarcinoma, in Barrett's esophagus and carcinoma of the esophagus, chronic hepatitis, hepatocellular carcinoma, cholangiocarcinoma, bill duct hyperplasia, adenocarcinoma and squamous cell carcinoma of the lung, actinic keratose and squamous cell carcinoma of the skin, malignancies and premalignancies of the breast, bladder, pancreas, head and neck.[6-11]

An enhanced expression of COX-2 is the result of increased transcription and stability of COX-2 mRNA[12] due to oncogenes, growth factors, cytokines, chemotherapy and tumor promoters. COX-2 is expressed as an early response[13] due to these factors. One possible mechanism of increased transcription of the COX-2 mRNA is the loss of wild-type p53, an inhibitor of transcription of COX-2 gene.[14]

In oral mucosal lesions, the expression of COX-2 protein increases from hyperplasia to dysplasia and is the highest in squamous-cell carcinoma.[15] Chan *et al.*[11] quantified the levels of COX-2 mRNA by RT-PCR and found that, in comparison to normal controls, COX-2 mRNA was increased 150-fold in the head and neck squamous-cell carcinoma and 50-fold in a normal appearing epithelium adjacent to cancer.

What are the precise COX-2 signaling pathways that promote tumorigenesis

COX-2 in carcinogenesis may include multiple mechanisms that may act at different stages of malignant disease. PGs, especially of the E series, induce cell proliferation, angiogenesis, invasion and metastases. Probably the most important role of COX-2 in tumorigenicity is enhancing angiogenesis of the tumor cells.[2] Angiogenesis is the prerequisite for tumor development and metastasis. Hypoxia, like in-growing tumor tissue, induces in vitro COX-2 expression, thereby also increasing the expression of the proangiogenic growth factor VEGF - vascular endothelial growth factor.[16]

Studies by Cianchi *et al.*[17] on 31 surgical specimens of colorectal carcinoma suggest that VEGF should be considered as one of the

most important factors involved in the stimulation of tumor angiogenesis promoted by COX-2 activity in colorectal cancer. These investigators found a significant correlation between COX-2 and VEGF mRNA levels as well as VEGF protein levels in the colorectal specimens. Gallo[18] showed that the COX-2 activation in epidermal tumor cell lines causes a rapid induction of VEGF mRNA and VEGF production in the neoplastic cells. COX-2 can also directly stimulate endothelial cell migration and growth factor induced angiogenesis with the production of eicosanoid products like TXA2, PGE2 and PGI2. Each of them is capable to stimulate the endothelial cell migration, tube formation, and induction of growth factors.[2]

COX-2 also inhibits endothelial cell apoptosis.[3] The pathogenetic pathway is the stimulation of Bcl-2 transcription.[3] Human microvascular endothelial cells that overexpress Bcl-2 are refractory to the apoptotic and angiosuppressive properties, and participate in more vigorous and sustained angiogenetic response.[19]

There are several studies on animal models that demonstrate these pathogenetic mechanisms. However, the recent clinical studies, where COX-2 expression was examined by immunohistochemistry, and correlated to clinicopathological features, are the most expressive. Tomozawa *et al.*[20] showed that COX-2 overexpression correlated with tumor recurrence and haematogenous metastasizing in colorectal cancer. In the study on esophageal squamous cell carcinomas by Kase *et al.*[21] COX-2 expression was associated with an increased intratumoral microvessel density and suppressed tumor cell apoptosis. In the study on renal cell carcinomas of 131 patients by Miyata *et al.*,[22] COX-2 immunohistochemical expression was significantly associated with various clinicopathological features (like high T, N, M stage in high tumor grade), with microvessel density and metalloproteinase-2 expression, but not with the apoptotic index (p= 0.054). In multivariate analysis, COX-2 expression was not a significant prognostic factor for survival; the disease stage stays the most significant determinant of patient's survival. The same significant positive correlations between COX-2 expression and lymph node metastases as well as histologic grade and tumor size were proved in the patients with breast carcinoma.[23]

COX-2 is also involved in the suppression of cell-mediated anti-tumor immune response. PGE2, probably the most damaging final products of COX-2 enzymatic action, inhibits, in vitro the production of tumor necrosis factor alpha and induces the production of interleukin-10,[24] a cytokine with immunosuppressive effects.

COX-2 also induces matrix metalloproteinase production via PGE2.[13] Matrix metalloproteinase enzymes degrade the type IV collagen of basement membrane and thus increase the invasiveness of tumor cells.

COX-2 may enhance the activation of procarcinogenesis - it can activate several classes of chemical carcinogens (aromatic and heterocyclic amines).[25]

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 selective inhibitors in human cancers

In the early 1990s, Thun *et al.*[26] showed in their study that regular aspirin use at low doses may reduce the risk of colon cancer. They speculated that this could be mediated through the inhibition of PG synthesis. Several studies were then performed on the use of other nonsteroidal anti-inflammatory drugs (NSAIDs), which are among the oldest and most widely used drugs. They reported about a 50-percent lower risk of colorectal cancer in people who are continuously taking these drugs.[27-29] Recent epidemiological studies found a significant inverse association be-

tween the intake of NSAIDs and the risk of breast cancer.[30,31] Meta-analysis of 14 epidemiological studies, analyzing the reduction of the risk for breast carcinoma with the use of NSAIDs was studied, showed that the regular use of NSAIDs was associated significantly with an 18-percent reduction in breast carcinoma.[32] Seven patients with head and neck squamous cell carcinoma (stages III and IV) were treated with different doses of indomethacin for 2 to 7 weeks.[33] Five of 7 patients demonstrated tumor regression; in 3 of them, it was significant. The patients who did not receive indomethacin showed no detectable response. The studies led to the identification of a molecular target, COX-2, involved in tumor promotion during colorectal cancer progression.[34-36] It was also discovered that NSAIDs did not suppress COX-2 expression or COX-2 protein level, but reduced its activity and inhibited PGE2 production.[37]

Encouraging results have now also been obtained with selective COX-2 inhibitors. Two different COX-2-selective inhibitors - rofecoxib and celecoxib - are currently available. Reddy *et al.*[34] reported that the administration of celecoxib to rats (male F344 rats with azoxymethane-induced colon carcinogenesis) during either stage of tumorigenesis inhibited the incidence as well as multiplicity of adenocarcinomas of the colon in a dose-dependent manner. It also suppressed colon tumor volume. This study provides the first evidence that celecoxib is very effective if given in the promotion or progression stage of colon carcinogenesis, indicating that chemopreventive efficacy is achieved during the later stages of colon tumor development. Also, the study on mice[35] showed that selective COX-2 inhibitor prevented hematogenous metastases of colon cancer. In addition to studies on colorectal carcinomas, the selective COX-2 inhibitor was used on human oral squamous cell carcinoma cell line (KB cells) implanted on the oral cavity of nude mice.[38] The significant reduction of tumor growth was observed and the number of microvessels, peripheral to the side of the tumor, was reduced. The study of Leahy *et al.*[39] on FGF-2 treated rodent corneas showed that the use of celecoxib at a dose of 30 mg/kg/day per os inhibited angiogenesis by 79%, and PGE2 production by 73%. A 65-percent decrease of proliferation and a 2.5-percent increase of apoptosis were observed.

The treatment with selective COX-2 inhibitors inhibited the COX-2 enzyme selectively and did not lower the gastrointestinal PG levels associated with mucosal protection. Celecoxib 400 mg twice daily effectively decreased the number and size of colon polyps in familial adenomatous polyposis with as little as 6 months of treatment;[40] however the dose of celecoxib 100 mg twice daily was not associated with significant regression in the size and number of polyps. Clinical evidence indicates that COX-2 selective inhibitors offer the therapeutic benefits of traditional NSAIDs with less of the associated toxicity.

Future directions

Recent studies in humans indicate that the therapy with specific COX-2 inhibitors might be an effective approach to cancer prevention and treatment. As the treatment with commonly used NSAIDs inhibit COX-1 and COX-2, the use of these agents may be limited by normal tissue toxicity, particularly that of gastrointestinal tract. Selective COX-2 inhibitors exert potent antiinflammatory activity but cause fewer undesired side effects. In both, the prevention of carcinogenesis and cancer therapy they may be more suitable as anticancer agents than standard NSAIDs. Based on the results of the study by Steinbach *et al.*,[40] US Food and Drug Administration approved celecoxib as adjuvant therapy for the patients with familial adenomatous polyposis (FAP). Similiarities between the biology of FAP and sporadic colorectal cancer suggest

that the strategies effective in FAP might be applicable also in the patients with colorectal adenoma. Several clinical studies are already under way to assess the efficacy of selective COX-2 inhibitors (celecoxib and rofecoxib) in preventing sporadic colorectal adenomas in large population.

Since COX-2 inhibitors protect against the formation of multiple tumor types in experimental animals, the potential utility on various target organs is also being examined. Therefore, cohorts of patients with Barrett's dysplasia, premalignant oral lesions, bronchial metaplasia, basal cell nevi and actinic keratosis are being treated.[1] COX-2 inhibitors could play a role in the chemoprevention of epithelial cancers.[13] COX-2 inhibitors could have an additive role also in the treatment of some breast tumors. In the breast cancer tissue, aromatase activity for the production of estrogens is enhanced via the increased expression of the aromatase CYP19 gene by PGE2,[41,42] which is increased by overexpression of COX-2 in neoplastic breast cells. The discovery that a selective COX-2 inhibitor suppresses aromatase activity would be very important since a large number of postmenopausal women who are at risk of breast cancer chronically use selective COX-2 inhibitors to treat artritis; thus an epidemiologic study should not be problematical.

In preclinical models, a selective inhibitor of COX-2 potentiated the beneficial antitumor effects of ionizing radiation with no increase in normal tissue antitoxicity.[43] A selective COX-2-inhibitor-induced enhancement of tumor radioresponse was associated with a decrease in PGE2 levels, inhibition of neoangiogenesis; however, there was no effect on radiation-induced apoptosis. This opens the possibility for the use of these drugs for the chemoprotection during the courses of ionizing radiotherapy. Recent evidence indicates that COX-2 also increases multidrug resistance protein1 (also known as P-glycoprotein), an efflux pump for chemotherapeutic agents.[44] This effect was prevented by the treatment with a selective COX-2 inhibitor.[44] Although much work is required to establish the clinical significance of this interaction, it is appealing to speculate that selective COX-2 inhibitors will enhance the antitumor activity of cancer chemotherapy by reducing multidrug resistance.[1]

Mohan and Epstein[13] discussed the use of COX-2 inhibitors in the head and neck squamous-cell carcinoma and proposed that this drug may represent a strategy for the prevention of displasia and cancer.

Although, the prevention and treatment with celecoxib seem promising, there are many obstacles that must not be overlooked. Selective COX-2 inhibitors have an excellent safety profile regarding gastrointestinal tract, but concerns have risen about cardiovascular safety.[45] The incidence of myocardial infarction has increased in the groups treated with Vioxx (rofecoxib) comparing with naproxen. By now, it is not certain whether this is a chance event, a pro-thrombotic effect of rofecoxib or a cardioprotective effect of naproxen. Further studies are needed.

Most likely, selective COX-2 inhibitors could become promising adjuvant therapy in the prevention and treatment of certain carcinoma, next to radiation and/or chemotherapy. It is most promising, too, that COX-2 inhibitor will be added to antiangiogenic chemotherapy. That clinical evaluation is urgently warranted. A possible indication for selective COX-2 inhibitor may also include secondary prevention of recurrent disease.

Conclusions

Combining the evidence from many studies, it may be concluded that the inhibition of COX-2 is a viable approach to cancer prevention and treatment. Despite these successes, many questions remain unanswered. Clearly,

research on COX-2 offers more hope of finding new approaches to the treatment of cancer.

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review

Survivin - an inhibitor of apoptosis and a new therapeutic target in cancer

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Survivin is a unique member of the inhibitor of apoptosis (IAP) protein family. It inhibits apoptosis by interfering with post-mitochondrial events during apoptosis, thus blocking activation of caspases. The expression of survivin is among the most tumour specific of all human genes. It is overexpressed in most human cancers but is not detected in most normal tissues. Some molecular mechanisms of survivin upregulation in cancer have been elucidated, including loss of the wild-type p53. Tumours that overexpress survivin generally bear a worse prognosis and are associated with resistance to therapy. Its differential expression in cancer versus normal tissues makes survivin detection a useful tool in cancer diagnostics and a promising therapeutic target. Survivin targeting has resulted in increased spontaneous and induced apoptosis and inhibition of tumour growth. Some anticancer drugs currently introduced into clinical practice might well act by inactivating survivin.

Key words: apoptosis - drug effects; caspases; protein p53; neoplasms

Introduction

Apoptosis, programmed cell death, maintains the homeostasis in tissues by regulating the balance between cell proliferation and cell death. A diminished ability of cancer cells to undergo apoptosis has been recognised as an important mechanism of tumour growth and progression. Failure to undergo apoptosis in the face of unrepaired damage leads to enhanced mutation, including chromosomal alterations, and can be a cause of the genomic instability that is a general characteristic of cancer progression.[1] Since the first description of apoptosis, three decades ago, as a special type of cell death with unique morphological characteristics, a complex genetic programme of cell suicide has been elucidated.[2,3]

In mammalian cells, apoptosis can be triggered either by extrinsic or intrinsic pathways. An extrinsic pathway is initiated by ligation of death receptors on the cell surface (CD95/Fas receptor, tumour necrosis factor-∝ receptor) and acts through the activation of initiator caspase 8. An intrinsic pathway is

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triggered by multiple death signals, either intracellular (unrepaired DNA damage) or environmental, that all culminate in dysregulation of the mitochondrial function. It results in an increased permeability of the outer mitochondrial membrane leading to release of mitochondrial proteins, including cytochrome c and SMAC/DIABLO. These proteins facilitate initiator caspase 9 activation, through a multiprotein complex called apoptosome (Figure 1).

Caspases, a family of cysteine proteases, are the key mediator molecules of apoptosis.[4] They are present in the cell as inactive precursors (procaspases) and are activated by proteolitic cleavage. Caspases are either initiator caspases (caspase 8 and 9) or effector caspases (caspase 3 and 7). Initiator caspases are activated by self-processing in multimeric protein complexes (such as apoptosome). Activated initiator caspases, in turn, cleave downstream effector caspases in a proteolytic cascade. Both intrinsic and extrinsic pathways converge to activate effector caspases. Finally, activated effector caspases specifically cleave cellular proteins that are involved in DNA repair, cytoskeletal organisation and nuclear integrity. This is the basis for morphological changes of apoptotic cells (nuclear fragmentation, condensation of the cytoplasm, detachment from the neighbouring cells, apoptotic bodies formation) and their clearance by phagocytosis.

Two gene families of apoptosis regulators have been identified - the Bcl2 family, and the inhibitor of apoptosis (IAP) family. Bcl2 proteins are thought to regulate mitochondrial

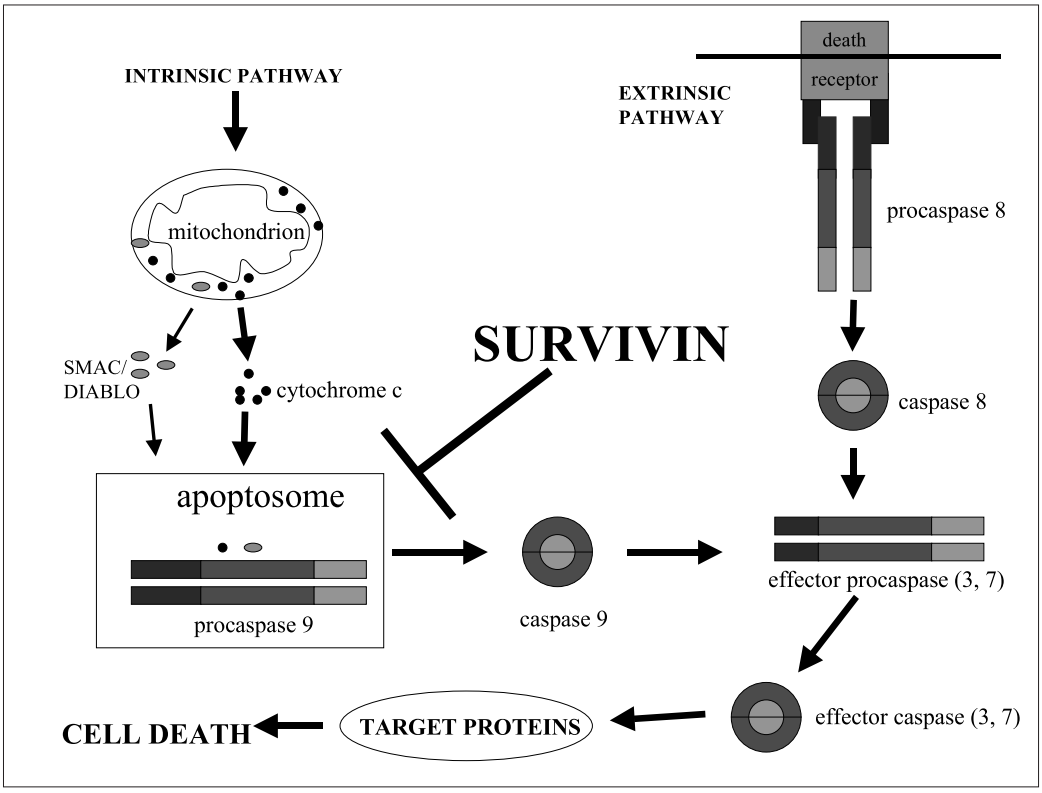

Figure 1. Apoptotic pathways and the site of survivin antiapoptotic action. Intrinsic and extrinsic apoptotic pathways are shown that converge into a common downstream pathway of effector capase activation. Survivin most probably blocks, directly and/or indirectly, caspase 9 activation.

permeability by either decreasing or enhancing the release of mitochondrial proteins, particularly cytochrome c, therefore modulating the intrinsic pathway of apoptosis. In contrast, IAP proteins possess only an inhibitory function and act downstream by preventing activation of caspase 9 in apoptosome and inhibiting the activity of effector caspases.[5]

Survivin is a unique member of the IAP family. It is of special interest because it is overexpressed in most human cancers but is not detected in most normal tissues. This fact makes survivin a molecular marker of cancer and a promising cancer therapeutic target.

Survivin structure and its subcellular distribution

Human survivin is a 16.5 kDa intracellular protein that belongs to the inhibitor of apoptosis (IAP) gene family. In humans, eight members of the IAP family have been identified, including NAIP, XIAP, c-IAP1, c-IAP2, Ts-XIAP, ML-IAP, Apollon and survivin. IAPs are characterised by carrying 1-3 copies of a 70-amino-acid zinc-finger fold, which is designated the baculovirus IAP repeat (BIR).[6] Survivin is the smallest IAP member, having a single BIR repeat and a homodimeric structure.[7] It consists of 142 amino acids, its gene spans 14.5kb at the telomeric position of chromosome 17 and has four exons and three introns.[8]

A single copy of the survivin gene gives rise to three alternatively spliced transcripts. In addition to wild-type survivin, two survivin isoforms are generated by the insertion of an alternative exon 2 (survivin-2B) or removal of exon 3 (survivin-ΔEx-3).[9] Because of the frameshift, the latter has a unique carboxyl terminus sequence containing a nuclear localisation signal, which is found exclusively in survivin-ΔEx-3 and may be implicated in subcellular targeting survivin to mitochondria and nucleus.[9,10] While survivin and survivin-ΔEx-3 are both antiapoptotic, survivin-2B has lost its antiapoptotic potential and might be a naturally occurring antagonist of antiapoptotic survivin variants.[10]

In mitosis, survivin has been shown to localise to various components of the mitotic apparatus, such as centrosomes and possibly microtubules. In tumour cells, the location of survivin is abnormal, with survivin present diffusely throughout the cytoplasm and often in the nucleus.[6,11]

Survivin shows a clear cell-cycle dependent expression at mitosis. This is largely controlled at the transcriptional level and mediated by cell-cycle dependent elements and cell-cycle homology regions that are located in the proximal survivin promoter. These regions are typically found in genes expressed in the G2/M phase of the cell cycle, such as cyclins A and B. In synchronised HeLa cells, transcription of the survivin gene is increased in G2/M by more than 10-fold, as compared to G1 or S arrested cells.[12] Polyubiqutylation and proteasome-dependent degradation at interphase and mitotic phosphorylation leading to increased stability at metaphase contribute to survivin accumulation at mitosis. Especially in non-transformed cells (CD34+ bone-marrow-derived stem cells, endothelial cells), survivin is upregulated in response to cytokine stimulation in a cell-cycle independent manner.[5] Endothelial cells upregulate their survivin expression after stimulation with vascular endothelial growth factor (VEGF).[6]

Survivin expression in normal and neoplastic tissues

Survivin expression has been extensively studied in neoplastic and non-neoplastic tissues by Western blotting, in situ hybridisation and immunohistochemistry. Survivin is strongly and diffusely expressed in embryonic and foetal organs, but is undetectable in most terminally differentiated normal tis-

sues. Adult normal cell types that express survivin include thymocytes, CD34+ bone-marrow-derived stem cells, endothelial cells, basal epithelial cells of colonic mucosa and epithelial cells of normal uterine cervix.[5,13] Week signals have been detected in placenta and proliferative and secretory endometrium.[8,14]

Notably, in contrast to normal tissues, survivin expression is dramatically upregulated in cancer, and survivin has been identified as the fourth trancriptome expressed in cancers of colon, lung, breast, brain and melanoma, but low or undetectable in the same normal organs.[7] An analysis of a panel of 60 different cancer cell lines revealed ubiquitous expression of survivin in all cell types, but at different levels.[12]

The molecular mechanisms of survivin overexpression in cancer seem to be complex and are only partially understood. Given the widespread survivin expression in many types of cancer, it is very likely that multiple pathways are involved in the reactivation of the survivin gene. There is compelling evidence that survivin overexpression does not simply reflect the presence of a higher number of proliferating cells, as the percentage of survivin positive cells in a tumour typically exceeds the number of proliferating cells measured by Ki67 labelling.[5]

Several molecular mechanisms implicated in survivin overexpression in cancer have been elucidated. In neuroblastoma, a frequent genetic abnormality is amplification of 17q25, containing the survivin locus.[15] Survivin exon 1 sequences are silenced by metilation in normal ovaries, but become unmetilated, and thus transcriptionally active in ovarian cancers.[7] Recently, wild-type p53, but not mutant p53, was shown to repress survivin expression in various human cancer cell lines.[16,17] A positive correlation between survivin expression and p53 accumulation (indicating its mutation) has been reported in gastric cancer[18], pancreatic adenocarcinoma[19], but not in transitional cell carcinoma of the upper urinary tract[20] or colorectal carcinoma.[21] Upregulation of survivin in colorectal cancer might result from APC (adenomatous polyposis coli) mutations.[5]

Survivin overexpression has been shown in preneoplastic lesions of the skin (actinic keratosis), pancreas (intraductal neoplasia), uterine cervix (intaepithelial neoplasia) and colonic adenomas, suggesting that survivin upregulation occurs early during tumourigenesis.[5,12,13,22,23] In colorectal carcinogenesis, there is a significant increase of survivin positive cases in transition from normal mucosa to adenoma with low dysplasia and from adenoma with low dysplasia to adenoma with high dysplasia.[24,25]

Three patterns of immunostaining to survivin are generally observed in tumour cells: 1. staining confined to the cytoplasm, 2. predominantly nuclear staining and 3. intense staining of mitotic figures (Figure 2). While early immunohistochemical studies reported the expression of survivin limited to the cytoplasm, subsequent studies also showed nuclear localisation of survivin. Differential subcellular localisation of survivin could reflect the presence of different survivin splice variants. Survivin and survivin-2B preferentially localise in the cytoplasm, whereas survivin-

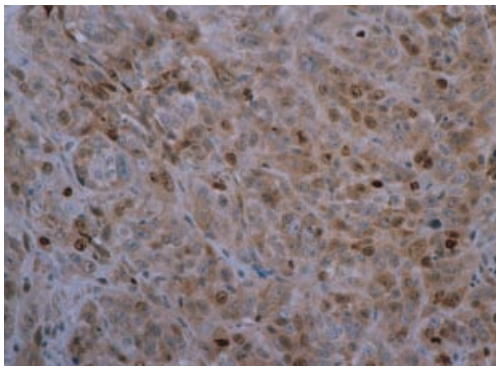

Figure 2. Immunostaining to survivin in hepatocellular carcinoma. Survivin is expressed in the cytoplasm and nucleus of tumour cells. Mitotic figures are intensely stained.

ΔEx-3 localises in the nucleus.[10] Nevertheless, results might be at least partially influenced by the use of different antibodies that recognise different epitopes. It is possible that the subcellular pools of survivin are immunohistochemically distinct, potentially reflecting post-translational modifications and/or epitope accessibility.[5]

Survivin function

The molecular mechanisms of survivin action are not fully elucidated and are, at least in some aspects, controversial. Nevertheless, it is a generally accepted view that survivin is an inhibitor of apoptosis and it interferes with cell-cycle progression and microtubule stability.

There is a huge body of experimental evidence characterising survivin as an inhibitor of apoptosis. In cell culture systems, overexpression of survivin has been consistently associated with inhibition of apoptosis initiated by both the extrinsic and intrinsic pathways.[5] Survivin counteracts apoptosis induced by certain chemotherapeutic drugs.[12] Apoptosis, either spontaneous or induced, is suppressed in organs and tissues of transgenic animals that express survivin.[5]

In general, mammalian IAPs block apoptosis by direct or indirect inhibition of terminal effector caspase 3 and 7 and initiator caspase 9.[6,12] There is no good evidence that survivin operates through direct contact with effector caspases. Recent studies suggest that survivin particularly inhibits the intrinsic pathway of apoptosis by interacting with post-mitochondrial events, as indicated by its ability to localize to mitochondria and to associate with caspase 9 and SMAC/DIABLO (Figure 1).[5,8,26]

In addition to its role in inhibiting apoptosis, survivin localisation to the mitotic apparatus indicates its role in cell division. Targeting survivin has resulted in aberrant mitotic progression, leading to failed cytokinesis and multinucleation.[5] Survivin is indispensable during embryonic development; its homozygous deletion in mice leads to inevitable lethality at day 4-5, due to defects in mitotic spindles formation.[6] The apparent requirement for survivin in normal cell division suggests that overexpression of survivin in tumours could perturb normal cell cycle control.

Survivin as a diagnostic and prognostic marker of cancer

Its differential expression in cancer, compared to most normal tissues, makes survivin a candidate for a molecular marker of cancer. Generally, survivin is (over)expressed in the majority of cases within a certain tumour type, the percent of positive cases ranging typically from approximately 30% to 100%.[12] Moreover, in retrospective trials, high survivin expression in tumours has been associated with shortened overall survival, an increased rate of recurrence and resistance to radiation and chemotherapy.[8,14,24,27,28] These data, in conjunction with a dual role of survivin in inhibiting apoptosis and promoting cell proliferation, indicate that survivin might confer growth and survival advantages for tumour onset and progression.[5] Indeed, an association between survivin expression and diminished apoptotic rates and/or higher proliferation activity has been reported.[14,24,27,28] There is good evidence that survivin is a powerful negative prognostic marker in most tumours studied. This fact might warrant a simple immunohistochemical detection of survivin in tumour specimens, which might provide a quick prognostic indicator for identifying patients at risk of recurrent disease and those who would benefit from more aggressive follow-up and alternative treatment protocols.[7]

Survivin can be detected in biological fluids of cancer patients, as a result of the shed-

ding of tumour cells from the primary sites. Survivin detection in the urine has proved to be a specific and sensitive marker of bladder cancer. Alternatively, circulating antisurvivin antibodies have been detected in cancer patients and detecting them could provide a potential diagnostic (screening) tool.[7]

Survivin as a therapeutic target

Survivin is an attractive therapeutic target because it is selectively expressed in cancer and is potentially required for the viability of cancer cells. A survivin-based anticancer therapy would be expected to carry limited toxicity for normal cells and to be effective in removing the general cell-viability system provided by survivin overexpression.[29]

Various approaches to targeting survivin have been tested *in vitro* and *in vivo*. Survivin synthesis (translation from survivin mRNA) can be blocked by using antisense technology and ribozymes. With the use of these approaches, loss of survivin expression can be sufficient to trigger apoptosis, to enhance chemotherapy-induced and radiotherapy-induced apoptosis and to dysregulate cell proliferation in tumour but not in normal cells.[5,30]

Experiments using phosphorilation defective survivin mutant Thr34→Ala revealed that phosphorilation of threonin at position 34 is required for cancer cell viability and might contribute to survivin stability at mitosis. Wild-type survivin is phosphorilated at Thr34 by mitotic kinase Cdc2-cyclin-B1. Survivin mutant Thr34→Ala functions as a dominant-negative mutant that competes with wild-type survivin, thereby blocking its activity. Adenoviral delivery of survivin Thr34→Ala suppressed tumour growth in cancer xenograft models *in vivo*.[6]

Survivin phosphorilation at Thr34 can be inhibited pharmacologically by recently developed antagonists of cyclin-dependent kinases, such as flavopiridol, which blocks cyclin-dependent kinases, including Cdc2.[5]

Recent observations suggest that T cells can mount a cytolytic response against survivin peptides and HLA class I restricted cytolytic T cells exist in patients with different cancers *in vivo*. A cancer specific immune response to survivin might therefore be used for potential vaccination strategies.[5]

Survivin is expressed in endothelial cells during angiogenesis and is associated with resistance to apoptosis. Ablation of survivin during angiogenesis caused endothelial cell apoptosis and promoted involution of three-dimensional capillary-like vessels *in vitro*. Therefore, by survivin targeting, tumour growth suppression could be at least partially mediated by inhibition of tumour angiogenesis.[7,31]

Conclusions

Survivin is an inhibitor of apoptosis and might be required for maintenance of cancer cell viability and cell-cycle progression. Its differential expression in cancer cells versus normal tissues has two important implications; it makes survivin a molecular marker of cancer and an attractive therapeutic target. Survivin is expressed in the majority of various cancers studied and, notably, it is generally considered a negative prognostic marker of cancer. Various strategies to targeting survivin in cancer cells are currently under investigation, giving promising results in *in vitro* and *in vivo* models. Moreover, some currently explored anticancer agents might mediate their anticancer effects by inhibiting the survivin pathway.

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Radiol Oncol 2003; 37(3): 141-53.

Deset let revije Radiology and Oncology nekaj bibliometrijskih izmer

Musek M, Oven M, Južnič P

Izhodišče. Bibliometrija s svojimi metodami predstavlja zelo koristen nabor orodij za analiziranje relativne pomembnosti strokovne revije znotraj njene stroke. S pomočjo kvantitativnih meritev vsebine in primerjavami s podobnimi revijami v stroki si tudi uredniki lahko pomagajo pri odločitvah glede nadaljnih usmeritev uredniške politike.

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Rezultati in zaključek. Rezultati kažejo, da se je revija dobro razvila, toda potrebni bodo dodatni napori ožjega uredništva in aktivna pomoč uredniškega odbora, da privabijo več kvalitetnih člankov in s tem povečajo njihovo število na zvezek, ter da postopoma povečujejo delež eksperimentalnih člankov, kar, kot kažejo izkušnje, lahko zviša relativni vpliv revije v stroki. Revija bi si lahko tudi povečala ugled tako, da bi vsi avtorji, ki v njej objavljajo, svoje objave v *Radiology and Onocology* smiselno vključevali med citate v članke, ki jih objavljajo drugje.

Radiol Oncol 2003; 27(3): 155-9.

Nepričakovana diagnoza predušesne otekline - prikaz dveh primerov

Roić G, Posarić V, Marušić A, Borić I, Vlahović T, Vrliček K

Izhodišča. Pri otrocih so lahko predušesne otekline povezane z najrazličnejšimi boleznimi. Anamneza, klinični znaki in slikovne preiskave so večkrat neznačilni. Pri načrtovanju preiskav moramo pomisliti tudi, da je vzrok takšne otekline sprememba na kosti.

Prikaz primerov. Poročamo o dveh primerih bolnikov, ki so bili napoteni v našo bolnico zaradi predušesne otekline in pri katerih smo nepričakovano ugotovili aneurizmalno kostno cisto in velikocelični granulom.

Zaključki. Pomembna je velika pozornost pri ugotavljanju vzroka takšnih predušesnih sprememb, da se izognemu napačni diagnozi in s tem tudi napačnemu zdravljenju. Rentgenološka preiskava večkrat ne zadošča. Ultrazvok z visoko ločljivostjo omogoča natančno preiskavo mehkih tkiv in pomaga pri diferencialni diagnozi ter omogoča natančno lokalizacijo bolezenske spremembe. Dodatna CT preiskava pa prikaže mesto, strukturo in velikost bolezenske spremembe.

Radiol Oncol 2003; 37(3): 161-5.

Ugotavljanje gnojnega hidradenitisa s transrektalno in transperinealno ultrazvočno preiskavo

Kołodziejczak M, Stefański R, Sudoł-Szopińska I, Jakubowski W

Izhodišča. Namen članka je predstaviti uporabnost transrektalne in transperinealne ultarzvočne preiskave pri ugotavljanju diferencialne diagnoze gnojnega hidradenitisa z analno fistulo.
Bolniki in metode. Pri 8 bolnikih, ki smo jim klinično ugotovili analno fistulo (6 bolnikov) ali gnojni hidradenitis (2 bolnika), smo naredili transrektalno in transperinealno ultrazvočno preiskavo, ker smo želeli natančneje opredeliti vnetne spremembe v analnem kanalu.
Rezultati. Pri vseh bolnikih je transrektalna ultrazvočna priskava pokazala ohranjene strukture analnega kanala, transperinealna preiskava pa je potrdila superficialno lokacijo patoloških sprememb.
Zaključki. Transrektalna in transperinealna ultrazvočna preiskava sta koristni za razlikovanje gnojnega hidradenitisa in analne fistule. Uporaba obeh metod omogoča natančno diagnozo.

Radiol Oncol 2003; 37(3): 167-74.

Pljučnica kot vzrok smrti pri bolnikih s pljučnim rakom

Zięba M, Baranowska A, Krawczyk M, Noweta K, Grzelewska-Rzymowska I, Kwiatkowska S

Izhodišča. Na bolnišničnih pljučnih oddelkih predstavlja pljučni rak resen klinični izziv. Pri mnogih bolnikih s pljučnim rakom je pljučnica sekundarni vzrok smrti in ne nastane samo zaradi napredovanja osnovne bolezni, ampak tudi zaradi stranskih učinkov zdravljenja, ki predstavljajo negativen vpliv na imunski odgovor organizma. Klinične in radiološke znake infekcijske bolezni si lahko napačno razlagamo kot napredovanje pljučnega raka. Tako je pri vsakem poslabšanju bolnikovega stanja izredno pomembno, da ugotovimo pravi vzrok poslabšanja, saj to bistveno vpliva na način zdravljenja.

Bolniki in metode. Retrospektivno smo analizirali 70 bolnikov, ki so umrli v letih 1997-1999 na Oddelku za tuberkulozo in pljučne bolezni Medicinske fakultete v £ůdüu zaradi pljučnega raka. Narejene so bile klinične in bakteriološke preiskave s posebnim poudarkom na ugotavljanju pljučnice kot vzroka smrti.

Rezultati. Pljučnico smo diagnosticirali pri 41 bolnikih s pljučnim rakom (58,5%) in streptokok pneumonije je bil najpogostejši etiološki dejavnik pljučne okužbe. Pri bolnikih z drobnoceličnim rakom pljuč sta obsežnost vnetnih sprememb na rentgenogramih in število leukocitov negativno korelirala s časom hospitalizacije ($R = -0,6$ in $R = -0,54$; $p<0,05$).

Zaključki. Čeprav predstavlja pljučni rak glavni vzrok smrti na našem Oddelku za tuberkulozo in pljučne bolezni Medicinske fakultete v £ůdüu, pa je bila pljučnica diagnosticirana v kar 58,5 % kot sekundarni vzrok smrti pri bolnikih s pljučnim rakom.

Radiol Oncol 2003; 27(3): 175-81.

Radioterapija pri bolniku z ne-Hodgkinovim limfomom testisa, stadij IAE - prikaz primera

Juretić A, Živković M, Gamulin M, Herceg T, Bagović D, Kučan D, Zeljko Ž, Ajduković R

Izhodišča. Namen članka je opisati obsevalno tehniko pri bolniku, ki smo ga zdravili zaradi primarnega ne-Hodgkinoveha limfoma (NHL) testisa, stadij IEA. Histološki izvid je pokazal, da je imel bolnik CD20 pozitiven NHL, oz. difuzno folikularen centrocitni (FCC) limfom, gradus III. Ker so primarni NHL-i redki, do sedaj ni bilo izdelanih splošno sprejetih načel, kako takšne bolnike obsevati. Bolezen NHL testisa poteka sorazmerno agresivno, zato so ponovitve bolezni pogoste tudi pri bolnikih, ki imajo zgodnji stadij bolezni (stadij I in II), in so bili po dosedanjih načelih optimalno zdravljeni (z orhiektomijo, polikemoterapijo in obsevanjem).
Prikaz primera. Bolniku smo ugotovili natančno diagnozo junija 2001, ko je bila narejena orhiektomija. Nato je prejel 6 krogov polikemoterapije (CHOP) in tudi intratekalno kemoterapijo z metotreksatom. Sledilo je obsevanje z enim direktnim poljem in z energijo 6 megavoltov na linearnem pospeševalniku. Obsevalno polje je obsegalo kontralateralni testis (skrotum) in ingvinofemoralne limfne bezgavke. Obsevalna doza je bila 30 Gy, ki smo jo aplicirali s 15 frakcijami in je bila določena na globini 4 cm. Zdravljenje z obsevanjem smo končali decembra 2001. Bolnika smo redno kontrolirali, tudi ob zadnjem pregledu maja 2003 je bil brez znakov bolezni.
Zaključki. Ker je ponovitev bolezni pri NHL testisov pogosta ekstranodalno ne pa v predelih limfnih bezgavk, ne moremo dokončno priporočiti, katere predele naj pri bolniku obsevamo.

Radiol Oncol 2003; 37(3): 183-6.

Dolgotrajno preživetje brez znakov bolezni pri bolnici, ki smo jo obsevali zaradi lokalno napredovalega pljučnega raka. Prikaz primera

Haraguchi N, Satoh H, Homma T, Sekizawa K

Izhodišča. Namen pričujočega zapisa je prikazati primer bolnice z dolgotrajnim preživetjem brez znakov bolezni po zdravljenju z obsevanjem lokalno napredovalega pljučnega raka.
Prikaz primera. 58-letno bolnico z velikoceličnim karcinomom pljuč in metastazami v vratnih bezgavkah smo zdravili z radikalnim obsevanjem. 9 let je bila brez znakov bolezni, nato pa smo ugotovili ponovitev bolezni lokoregionalno in z oddaljenimi zasevki.
Zaključki. Kljub dolgotrajnemu preživetju brez znakov bolezni moramo bolnike z nedrobnoceličnim rakom pljuč kontrolirati vse življenje. Priporočamo skrbno spremljanje bolnikov s povečanim tveganjem ponovitve bolezni.

Radiol Oncol 2003; 37(3): 187-94.

Vloga ciklooksigenaze-2 v malignem tkivu in možnosti uporabe njenih zaviralcev v zdravljenju raka

Mateja Legan

Encim ciklooksigenaza-2 je inducibilna prostaglandinska sintaza. Njeno povečano izražanje so opisali v številnih premalignih in malignih tkivih. Preko povečanega sproščanja prostaglandinov pospešuje karcinogenezo, tako da pospeši tumorsko angiogenezo, zavira apoptozo, aktivira matriksne metaloproteinaze. Zavira tudi celično posredovan antitumorski imunski odgovor in ščiti pred poškodbami s citotoksičnimi učinkovinami. Cikloosigenaza-2 je lokalizirana v neoplastičnih epitelijskih celicah, endotelijskih celicah novonastalega tumorskega žilja, v fibroblastih in vnetnih celicah tumorske strome. Dokazi iz študij *in vitro*, raziskave na živalskih modelih ter prvi klinični rezultati kažejo, da zaviralci COX-2 lahko upočasnijo karcinogenezo z zaviranjem angiogeneze, zmanjšanjem invazivnosti tumorja in pospeševanje apoptoze tumorskih celic. Rezultati nakazujejo možno in zelo verjetno vlogo zaviralcev COX-2, predvsem selektivnih zaviralcev COX-2, v zdravljenju raka kot dodatna (adjuvantna) terapija, oz. *so-kemoterapevtik*, tako v primarni preventivi, zdravljenju kot tudi zaščiti pred ponovitvijo bolezni. Namen preglednega članka je predstaviti spoznanja o vlogi ciklooksigenaze-2 v malignem tkivu ter poiskati terapevtsko mesto zaviralcev COX-2 v klinični praksi.

Radiol Oncol 2003; 37(3): 195-202.

Zaviralec apoptoze survivin kot tarča ciljanega zdravljenja raka

Pižem J, Cör A

Survivin sodi v družino beljakovin zaviralcev apoptoze (inhibitor of apoptosis, IAP). Zavira aktivacijo kaspaz, tako da vpliva na »po-mitohondrijske« dogodke med apoptozo. Survivin se (prekomerno) izraža v večini tumorjev, v normalnih tkivih pa ne. Poznani so nekateri molekularni mehanizmi, ki so odgovorni za prekomerno izražanje survivina v tumorjih, eden takih je izguba divjega tipa beljakovine p53. Tumorji, ki izražajo survivin, so v splošnem manj občutljivi na zdravljenje, preživetje bolnikov je slabše. Zaradi različnega izražanja survivina v tumorskem in netumorskem tkivu je survivin uporaben v molekularni diagnostiki tumorjev, hkrati pa primerna tarča za razvoj takšnega načina zdravljenja, ki je usmerjeno proti tumorju in čim manj poškoduje normalna tkiva. Zaviranje delovanja survivina vodi v povečano spontano ali sproženo celično smrt (apoptozo), kar zavre rast tumorja. Nekatera novejša zdravila proti raku verjetno delujejo v veliki meri preko zaviranja delovanja survivina.

Radiol Oncol 2003; 37(3): 203-8.

Notices

Notices submitted for publication should contain a mailing address, phone and/or fax number and/or e-mail of a ***Contact*** *person or department.*

Radiation therapy

October 19-23, 2003

ASTRO Annual meeting will be held in Salt Lake City, Utah, USA.

Contact American Society for Therapeutic Radiology and Oncology Office, 1891 Preston White Drive, Reston, VA 20191, USA; or see http://www.astro.org

Breast cancer

November 1-5, 2003

The »24th Congress of the International Association for Breast Cancer Research« will be offered in Sacramento, California, USA.

Contact Continuing Medical Education UCDAVIS School of Medicine, 3560 Business Drive, Suite 130, Sacramento, CA 95820, USA; or call +1 916 734 5390; or fax +1 916 453 9429.

Pleural mesothelioma

November 7-8, 2003

The international conference will be offered in Como, Italy.

Contact ASK, International Conference Como 2003, Via Tabacchi, 20, 21056 Induno Olona (VA), Italy; or call +39 0332 840650; or fax +39 0332 204028; or e-mail ask@skylink.it

Lung cancer

November 8, 2003

The international conference »Lung Cancer Screening and Early Diagnosis« will be offered in Como, Italy.

Contact ASK, International Conference Como 2003, Via Tabacchi, 20, 21056 Induno Olona (VA), Italy; or call +39 0332 840650; or fax +39 0332 204028; or e-mail ask@skylink.it

Radiation oncology

November 9-14, 2003

The ESTRO teaching course »Evidence-Based Radiation Oncology: Methodological Basis and Clinical Application« will take place in Lisbon, Portugal.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Radiation oncology

March, 2004

The ISRO international teaching course on »Radiation Oncology in the 21st Century« will take place in Cape Town, South Africa.

See http://www.isro.be

Surgical oncology

March 31 - April 3, 2004

The 12th ESSO Congress will be held in Budapest, Hungary.

See http://www.fecs.be/conferences/esso2004

Oncology

April 15-17, 2004

The European Oncology Nursing Society EONS Spring Convention will be held in Edinburg, UK.

See http://www.fecs.be/conferences/eons4

Brachytherapy

May 13-15, 2004

The Annual Brachytherapy Meeting GEC-ESTRO will take place in Barcelona, Spain.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Radiology

June 6-8, 2004

The UK Radiological Congress will be held inManchester, U.K.

Contact Ms. Rebecca Gladdish, UKRC 2003 Secretariat, PO Box 2895, London W1A 5RS, U.K., or call +44(0) 20 7307 1410/20, or fax +44(0) 20 7307 1414; or e-mail conference@ukrc.org.uk/exhibition@ukrc.org.uk; or see www.ukrc.org.uk

Oncology

July 3-6, 2004

The 18th EACR (European Association for Cancer Research) Congress will be held in Innsbruck, Austria.

See http://www.fecs.be/conferences/eacr18

Paediatric oncology

September, 2004

The International Society of Paediatric Oncology - SIOP Annual Meeting will be held in Oslo, Norway.

See http://www.siop.nl

Lung cancer

September 23-25, 2004

The »9th Central European Lung Cancer Conference« will be offered in Gdansk, Poland.

Contact Conference Secretariat, »9th Central European Lung Cancer Conference«, Via Medica, ul. Swietokrzyska 73, 80 180, Gdansk, Poland; or call/fax +48 58 349 2270; or e-mail celcc@amg.gda.pl; or see www.lungcancer.pl

Radiation therapy

October 3-7, 2004

ASTRO Annual meeting will be held in Atlanta, USA.

Contact American Society for Therapeutic Radiology and Oncology Office, 1891 Preston White Drive, Reston, VA 20191, USA; or see http://www.astro.org

Therapeutic radiology and oncology

October 24-28, 2004

The 23rd ESTRO Meeting will be held in Amsterdam, the Netherlands.

Contact ESTRO office, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium; or call +32 7759340; or fax +32 2 7795494; or e-mail info@estro.be; or see http://www.estro.be

Medical oncology

October 29 - November 2, 2004

The 28th ESMO Congress will be held in Vienna, Austria.

See http://www.esmo.org

Radiation oncology

November 25-28, 2004

The ISRO international teaching course on »Practical Radiation and Molecular Biology with Mayor Emphasis on Clinical Application« will take place in Chiangmai Thailand.

See http://www.isro.be

Radiation oncology

March, 2005

The ISRO international teaching course on »Palliative Care in Cancer Treatment« will take place in Dar es Salaam, Tanzania.

See http://www.isro.be

Radiation oncology

September - October, 2005

The ISRO international teaching course on »Rational Developments from developing to developed Countries« will take place in Lombok, Indonesia.

See http://www.isro.be

Oncology

October 30 - November 3, 2005

The ESTRO 24 / ECCO 13 Conference will take place in Paris, France.

Contact FECS office, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium; or call +32 7759340; or fax +32 2 7795494; or e-mail info@estro.be; or see http://www.fecs.be

As a service to our readers, notices of meetings or courses will be inserted free of charge.
Please send information to the Editorial office, Radiology and Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia.

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Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education – A Report for the Third Quarter of 2003

The regular annual meeting of the general assembly of the "Dr. J. Cholewa Foundation for Cancer Research and Education" on June 5th, 2003, started with a sombre note. The assembly participants paid their respects to Mr. Srečko Mihelčič, Professor Vinko Kambič and Mr. Metod Rotar, all of them founding members of the Foundation. All three long time and important members of the Foundation passed away in the year 2002 and all left an indelible mark on the Foundation's activity and its character. Srečko Mihelčič was a great promoter of the Foundation's activities and an important donor of the Foundation in general. His kindness, his wit and his propensity for all new ideas coming out on the Foundation's meetings and elsewhere will be greatly missed. Professor Vinko Kambič was a member of the Slovenian Academy of Sciences and Arts and one of the most important figures in medicine and public life in general in Slovenia. His important role in the development and functioning of the Foundation cannot be overstressed. Metod Rotar was a senior figure and a doyen of the Slovenian banking in the last decades. His broad-mindedness and simultaneous simplicity, both characteristics of great men, made him indispensable for the Foundation. The Foundation remains grateful for all their contributions to its activity and obliged to their memory.

Reports of the Administrative and Supervising Boards of the Foundation and the report by the Health experts Commission of the Foundation were also presented at the annual meeting of the general assembly. The reports included the detailed business and financial reports. The Foundation will continue to support the regular publication of "Radiology and Oncology" international scientific journal, which is edited, published and printed in Ljubljana, Slovenia. The Foundation will also continue in its activity to promote cancer biology research, research in cancer epidemiology and clinical cancer research in their many different pathways. Several new members were also admitted to the Foundation on that occasion, including Professor Blaž Mlačak, Professor Janez Fischinger, Dr. David Dovšak, Ms. Branka Cimerman, and Dr. Ana Hinterlechner-Ravnik and Dr. Daniel Ravnik, both as life members of the Supervisory Board of the Foundation.

At the same time the Foundation expressed its deep gratitude to dr. Ana Hinterlechner-Ravnik for her important contribution to the Foundation, dedicated to the memory of her late sister, ms. Teja Lavrič, Univ. Dipl. Ing.. A memorial "Dr. J. Cholewa" plaque and a charter on the behalf of the Foundation were presented to dr. Ana Hinterlechner-Ravnik by Mr. Slavko Fatur, the President of the "Dr. J. Cholewa Foundation for Cancer Research and Education" for her magnanimous and graceful deed.

An interesting development may also take place in the near future with the Foundation possibly coming to agreement with KRKA pharmaceutical company from Novo Mesto in southern Slovenia. These initial steps in the possible future collaboration include the consideration of ideas about cancer research activity to be performed by some of the young researchers from this well-known and reputed pharmaceutical company.

Tomaž Benulič, MD
Borut Štabuc, MD, PhD
Andrej Plesničar, MD

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Datum priprave besedila: marec 2003

Podrobnejše informacije so na voljo pri proizvajalcu.

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DAKO (Danska):
testi za aplikacijo v imunohistokemiji, patologiji, mikrobiologiji, virologiji, mono- in poliklonalna protitelesa

SVANOVA Biotech (Švedska):
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GFL (Nemčija):
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ANGELANTONI SCIENTIFICA (Italija):
hladilna tehnika in aparati za laboratorije, transfuzijo, patologijo in sodno medicino

EHRET (Nemčija):
laminar flow tehnika, inkubatorji, sušilniki, suhi sterilizatorji in oprema za laboratorijsko vzrejo živali - kletke

INTEGRA BIOSCIENCES (Švica):
laboratorijska oprema za mikrobiologijo, biologijo celic, molekularno biologijo in biotehnologijo

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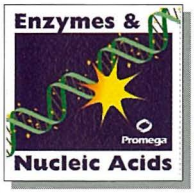

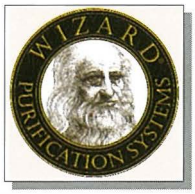

IZDELKI ZA MOLEKULARNO BIOLOGIJO

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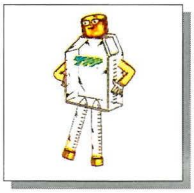

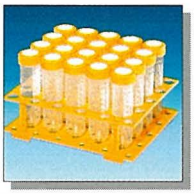

PLASTIKA ZA CELIČNE KULTURE

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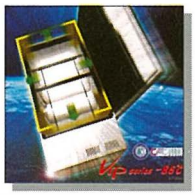

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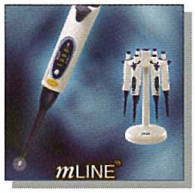
BIOHIT



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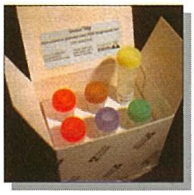


DIAGNOSTIKA MIKOPLAZEM IN LEGIONEL

LI-COR Biosciences

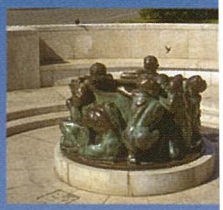
SEKVENATORJI

Croatian Society for Ultrasound in Medicine and Biology

European Federation of Societies for Ultrasound in Medicine and Biology







EUROSON 2004

Highligths

General US (gastroenterology, nephro-urology, breast, head and neck, pediatrics), Gynaecology and Obstetrics, Musculoskeletal US, Vascular US, Surgical and Interventional US (endoluminal, intra-operative US, laparoscopic US and tissue ablation) New Technology and Physics (contrast agents, harmonics, 3D, B-flow, bioeffects and safety, and others), Sonography, Veterinary US, Miscellaneous

Pre-congress events

Thomas Jefferson LIniversity - Recent advances in ultrasaund, Contrast agents in ultrasound, IBUS course, Doppler of Arterial and venous circulation, Ultrasonography and endascopy in cholostasis, Gynaecological Ultrasound and human reproduction, New developments in ultrasound assessment of pelvic mass, Ultrasound in perinotolgy, Ultrasound in veterinory medicine, Endoscopic ultrasound, US course

Program

Plenary sessions:

Breost ultrosound, General Abdomen, Neck ond Thyroid glond, Pediatric US, Doppler Periphery, Ultrasound in perinatology, Interventional and intro-operative ultrasound, Ultrosound in cardiology, Musculoskeletal ultrosound, Orthopedics and sport injuries, Carotid arteries and TCD, TCD ond contrast doppler in neurology, Ultrasound in gynaecology and human reproduction, Physics of ultrasaund, Ultraosound in veterinary medicine, Ultrasound of thorax, Urogenital ultrasound, Ultrasound in Ophtalmology, Ultrasound in emergency, Safety of Ultrasound, Young investigators session

Teaching sessions:

Contrast agents and breast color doppler, GI ultrasound, Ultrasound of childrens hips, Parathyroid glond and ultrasound, Renal doppler, RF ablation, 4D echocardiography, Ultrasound in Veterinary medicine

Workshops:

Locomotive system, Needle biopsys, Carotid arteries, Mammotome biopsy, Termoablation RF, Vein Doppler, TCD Doppler, 4D Doppler

Lunch symposiums, Poster sessions, Meeting with the Professor session

Invited speakers

J.R.T.C. Roelandt - V.Mitkov - N.Drinković - I.Čikeš - S. Ernst - B. Goldberg - L. Greiner - C. Dietrich - N. Juul - B. Limberg - D. Nürnberg - H.P. Weskott - A. Bunk - Meckler - Benhof - I. Sporea - W.Jakubowski - I. Lukač - E. Zerem - M. Duvnjak - T. Helemberger - D. Giatini - L. Bolondi - D. Amy - M. Teboul - W. Svenson - B.Salvadori - I. Drinković - D. Francescatti - L. Derchi - C. Martinoli - S. Costellani - B. Brkljačić - V. Demarin - S. Podobnik - E. Halpern - L. Needleman - K. Jäger - D.H. Evans - L. Boromo - L. Nazorin - J. Vrdoljak - G. Harmat - A. Vargha - Z. Harkany - E. Mertz - J.B. Hackeloer - D. Jurković - V. Vlaisavljević - M. Podobnik - Z. Sretenović - A. Kurjak - S. Kupešić - P. Wells - B. Phillips - B. Breyer - L. Chitty - D. Pilling - L. Bonoma - M.Teboul - R. Otto - M. Claudon - M.B. Nielsen - C. Weismann - G.M. Reutern - N.M. Bornstein - A. Alexandrov - K. Niederkorn

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Each course will allow a maximum of 20 participants.
Registrations will be accepted on a first come first serve basis, however, EANM members will be given relative priority.

Please download and print out the registration form from our homepage www.eanm.org and fax it back to the EANM-secretariat.

Goals and curriculum

EANM has established the PET learning facility in order to provide the highest standard of education on PET and its relation to other imaging modalities in Europe. A reknowned faculty was asked to prepare powerpoint presentations and case studies to cover all pertinent areas of PET.

At each course instructors will cover the presentations and case studies in "classroom style" in the lecture room. There will also be ample time for participants to view case studies in 4 viewing rooms, equipped with state of the art multipurpose viewing stations. One "industry viewing room" features workstations by all three major manufacturers of PET equipment.

For all further information on the EANM learning courses on clinical PET please contact:

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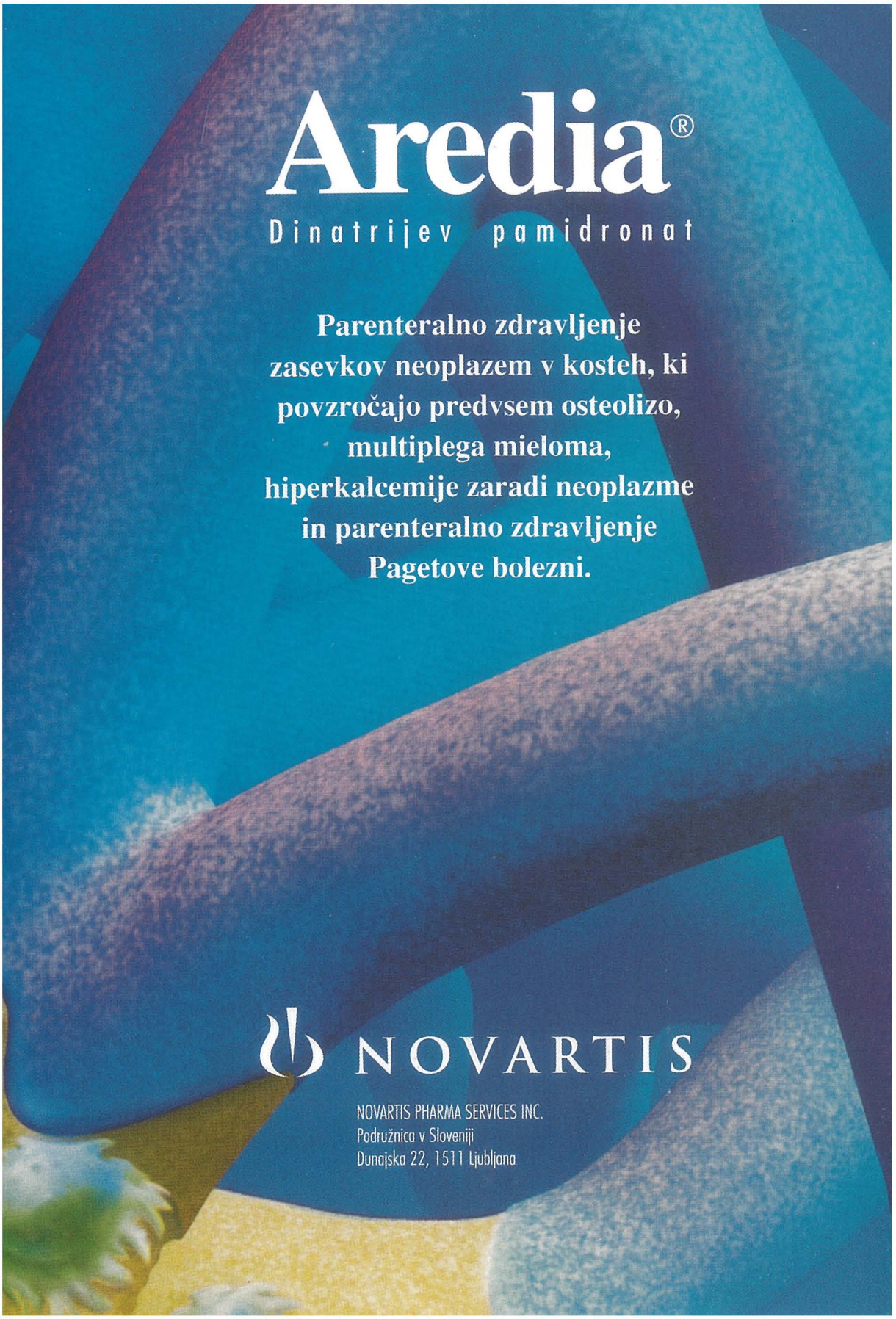
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